Management of Rabies in Humans

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Rabies is a fatal disease in humans, and, to date, the only survivors of the disease have received rabies vaccine before the onset of illness. The approach to management of the rabies normally should be palliative. In unusual circumstances, a decision may be made to use an aggressive approach to therapy for patients who present at an early stage of clinical disease. No single therapeutic agent is likely to be effective, but a combination of specific therapies could be considered, including rabies vaccine, rabies immunoglobulin, monoclonal antibodies, ribavirin, interferon-α, and ketamine. Corticosteroids should not be used. As research advances, new agents may become available in the future for the treatment of human rabies.

Indigenous or imported cases of human rabies occur sporadically in developed countries, and human rabies remains an important public heath problem in developing countries [1]. Rabies postexposure prophylaxis, which is highly effective if given promptly, includes wound cleansing, immunization with a modern cell-culture vaccine, and administration of human rabies immunoglobulin (HRIG) [2]. Once rabies encephalitis develops, no therapy has proved effective. A working group considered potential treatment options in the management of human rabies. The following discussion of the management of rabies was designed for physicians who are faced with caring for a patient with probable or confirmed rabies.

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AGGRESSIVE OR PALLIATIVE APPROACH TO THERAPY?

The management of patients with rabies should be influenced by a review of the available clinical data for patients who were treated aggressively in critical care units. A large number of case reports but only a few series of treated patients have been published [3]. In all of these reports, only 5 of the patients mentioned survived their acute illness [4–9]; only one of them had a satisfactory neurologic outcome [4], and another died within 4 years as a result of complications of the severe neurologic sequelae [8, 10]. There may be debate as to whether some of these patients actually had rabies. Postvaccination encephalomyelitis (due to vaccine of nervous tissue origin) is a possibility in $\geqslant$1 of the patients described [7]. All of these possible survivors had received a rabies vaccine either before or soon after their exposure and before the onset of their illness. None of these patients had rabies virus isolated or rabies virus antigen detected.

Even with intensive care, the majority of patients with rabies do not survive for >3 weeks [11], although 1 patient died 133 days after the onset of illness [12]. For previously unvaccinated patients with rabies, reports to date have indicated agonizing symptoms and a 100% mortality rate. This record offers little encouragement for heroic efforts. In view of the poor prognosis, routine management of patients with rabies should be palliative. Complications of the disease should be anticipated, and appropriate steps for their prevention or treatment should be taken. Neurological symptoms and medical complications may be alleviated by the use of sedatives, narcotic analgesics, antiepileptic medications, and neuromuscular blockers. Barrier nursing techniques should always be used to prevent exposures of health care workers or family members during management of a patient with rabies. However, transmission of rabies virus to a health care worker has not been documented to date.

In unusual circumstances, the attending physicians and the patients (or, more

commonly, their relatives) may wish to use an aggressive approach to therapy with the aim of curing the disease. However, it must be clearly understood that even if such an approach were successful, the patient likely would be left with permanent disabling neurological deficits. The following patient characteristics and resources could be considered favorable in making the decision to embark on an aggressive course of therapy:

1. Administration of any rabies vaccine before the onset of clinical rabies.
2. Presentation with a very early stage of disease, including paresthesias or pain at the site of a previous bite exposure, with minimal other neurological symptoms or signs.
3. Good health and absence of chronic disease.
4. Relatives who accept both the high probability of an unsuccessful outcome and the possibility of disabling neurological deficits in a rabies survivor.
5. Access to adequate resources and facilities.

Early diagnosis of rabies, with or without laboratory confirmation, is important for the prevention of exposures of health care workers and for initiation of specific therapy if an aggressive approach is considered. Patients with rabies may present without a history of an animal bite or exposure, especially in the United States [11]. Early clinical features of rabies are nonspecific prodromal symptoms and local neurological symptoms, including paresthesias, pain, and pruritus at the site of virus entry, and 61% (54 of 88) of the cases reported in the United States during 1957–2000 were associated with these neurological symptoms [10, 13]. The clinical presentation of rabies evolves into either encephalitic (furious) or paralytic (dumb) forms of the disease. Hyperexcitability, autonomic dysfunction, and hydrophobia are characteristic of encephalitic rabies, and quadriparesis with sphincter involvement is characteristic of paralytic rabies [10]. At an early stage of the illness, results of diagnostic tests for rabies [2] may not yet be positive or may be unavailable, but this should not delay initiation of therapy if there is strong clinical evidence in support of a diagnosis of rabies. Patients considered for aggressive care must be admitted to a hospital where there is access to a critical care unit with sophisticated modern medical technology and skilled medical and nursing personnel, in anticipation of the development of multiple medical complications, including multiple-organ failure [14].

COMBINATION THERAPY

Therapy with a single agent, such as ribavirin or IFN-α, has been unsuccessful [15, 16], although it is possible that a combination of specific therapies may be more effective. This approach—with the use of, for example, vidarabine and IFN—has been tried for patients with a late stage of disease [17]. Combinations of therapies are also being used for the treatment of other viral diseases. Ribavirin and IFN-α provide a clinically synergistic effect in the treatment of chronic hepatitis C infection [18, 19]. For example, combination therapy for a patient with rabies might include administration of rabies vaccine (multiple-site intradermal route), HRIG (intramuscular), ribavirin (intravenous and intraventricular via Ommaya reservoir), IFN-α (intravenous and intraventricular via Ommaya reservoir), and ketamine (intravenous infusion).

SPECIFIC THERAPIES

Rabies vaccine. Intramuscular administration of rabies vaccine in an attempt to stimulate humoral and cellular immune responses has frequently been performed without apparent benefit. Rabies encephalitis survival among animals is associated with an immune response. Rabies immunization may therefore be a reasonable approach to use in combination with other therapies. Because immunization by the intramuscular route may take a week or more to produce detectable immune responses, multiple-site (e.g., 8 or 4 sites) intradermal immunization [20] should be considered to accelerate the response. Human rabies vaccines are inactivated and do not elicit a cytotoxic T cell response, which is observed with live attenuated or recombinant rabies vaccines for animal use and which may be important for virus clearance [21]. Experimental vaccines that induce potent cytotoxic T cell responses are undergoing preclinical testing and might provide treatment options for the future. No human live attenuated or recombinant rabies vaccine has been licensed for use in humans to date.

Rabies immunoglobulin. Administration of HRIG to a patient with clinical rabies would have the aim of promoting clearance of the infection, although, experimentally, only a monoclonal antibody has proved effective (see the "Monoclonal antibodies" subsection below). In contrast, in rabies postexposure prophylaxis, HRIG neutralizes the virus before its invasion of the nervous system. However, because immunoglobulins do not normally cross an intact blood-brain barrier [22], it is uncertain to what extent the immunoglobulins would enter the CNS in rabies and whether they would produce a significant effect in clearing the infection. An option is intramuscular administration of the same dosage of HRIG used for postexposure rabies prophylaxis (20 IU/kg); it is uncertain whether higher doses might have greater efficacy. Because the use of massive doses of HRIG would lead to wasting of biologics that are in limited supply and that are important for rabies postexposure prophylaxis, this treatment option should not be pursued. The efficacy and safety of intrathecal administration of HRIG are unknown. Equine rabies immunoglobulin could be used instead of HRIG in situations in which HRIG is not available.

Monoclonal antibodies. Administration of rabies virus–neutralizing monoclo-

nal antibodies (e.g., monoclonal antibody 1112-1) has been shown to clear rabies virus infection from the CNS in a rodent model when administered before the onset of clinical signs, resulting in the survival of experimentally infected rats [23]. This suggests that therapy with ⩾1 monoclonal antibodies may prove to be effective therapeutically in the future. Human monoclonal antibodies or humanized mouse monoclonal antibodies would be preferable to mouse monoclonal antibodies. Evaluation of this strategy would require development of an investigational drug protocol.

Ribavirin. Ribavirin (1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide) is a broad-spectrum antiviral agent with many intrinsic mechanisms that can influence its overall antiviral properties [19]. Ribavirin is a purine analogue and an RNA mutagen that induces mutations by acting as a template for incorporation of cytidine and uridine with equal efficiency [24]. Ribavirin also has immunomodulatory properties that may, in part, account for its antiviral properties in vivo [25]. Ribavirin has in vitro activity against rabies virus infection [26, 27], although efficacy was not demonstrated in a study that used animal models [28]. Ribavirin is typically administered intravenously with both loading and maintenance doses. There is limited information about its penetration across the intact blood-brain barrier, which may be marginal, because rapid uptake into CSF was not observed in rats and rhesus monkeys [29]. However, significant levels of ribavirin were observed in CSF after orally administered ribavirin therapy was given for several weeks to patients with AIDS and AIDS-related complex [30]. Intraventricular administration of ribavirin via an Ommaya reservoir, in addition to therapy by the intravenous route, would be a therapeutic option at the present time. One patient with rabies who was treated with a combination of intrathecal and intravenous ribavirin therapy demonstrated no apparent benefit [16].

IFN-α. IFN-α is a natural immunoregulatory protein and an immunotherapeutic drug for viral and neoplastic diseases [31]. IFNs provide a first line of defense against viral infections by generating an intracellular environment that restricts viral replication. IFN-α interacts with cells of the innate immune system and participates in the transition to an effective adaptive-immune response, including antigen presentation for activation of cytotoxic T cell responses [31]. IFN-α may also act synergistically with antibody, which has been demonstrated in Sindbis virus infection [32]. The efficacy of therapy with IFN-α has been demonstrated in studies of rabies virus–infected monkeys [33]. However, 3 patients with rabies, who were treated at an early stage of the disease with a combination of high doses of intrathecal and intravenous therapy with IFN-α, experienced no beneficial effect [16].

Ketamine. Ketamine is a dissociative anesthetic agent and a noncompetitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor. Ketamine has sedative and analgesic properties, and it rapidly crosses the blood-brain barrier [34]. At high concentrations (1–2 m*M*), ketamine has been demonstrated to inhibit the in vitro replication of rabies virus by inhibiting rabies virus genome transcription [35]. After stereotaxic inoculation of a strain of fixed rabies virus in the neostriatum of rats, administration of high-dosage ketamine (60 mg/kg ip q12h) led to reduced infection in multiple brain regions, including the hippocampus, cerebral cortex, and thalamus [36]. In addition, the topographic distribution of rabies virus in the brains of infected rodents suggests that NMDA receptors may be a receptor for rabies virus [37]. For these reasons, ketamine may be considered a potential therapeutic agent in the management of human rabies, although it is unlikely that achievable drug levels would exert an antiviral effect. Ketamine may be administered as a continuous intravenous infusion in a critical care setting [34].

Corticosteroids. In mouse models, administration of corticosteroids increased the mortality rate and shortened the incubation period [38]. Corticosteroid therapy generally is not considered for the management of brain edema in rabies. Severe edema associated with a risk of brain herniation is rare in patients with rabies, although this is a potential complication of intrathecal therapy with HRIG [39]. Administration of corticosteroids therefore is not recommended for rabies therapy, except for treatment of adrenocortical insufficiency. Therapy with corticosteroids may not be desirable for complications that are possibly immunopathogenetic, such as myocarditis in rabies. In addition, corticosteroids may effectively close the blood-brain barrier and reduce the entry of other therapeutic agents.

SUMMARY

The dismal outcome of patients with rabies provides little optimism for heroic efforts. Palliative therapy is of paramount importance in this fatal disease. There may be situations in which an aggressive approach is desirable, in particular during a very early stage of the disease, although the probability of failure is very high. Combination therapy may be superior to therapy with a single agent. Specific treatments for consideration at the present time include rabies vaccine, HRIG, ribavirin, IFN-α, and ketamine. Therapy with corticosteroids should be avoided. A greater understanding of the pathogenesis of rabies may, in the future, lead to the development of new agents with therapeutic efficacies that could be demonstrated in relevant animal models.

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