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Worldwide, human rabies continues to be an important public health problem with about 55,000 human deaths each year; most cases occur in Asia and Africa (1). As human rabies transmitted from dogs has become under control in Latin America, the problem of transmission from vampire and insectivorous bats becomes more apparent. Prevention of rabies in rabies vectors and in humans after exposures is extremely important. But when these steps fail, physicians are faced with a very difficult medical management problem, which was recently comprehensively reviewed by a group of clinicians with expertise in rabies and basic researchers in the pathogenesis of the disease (2). Combination therapy was recommended based on successes in other diseases, including cancer, human immunodeficiency virus infection, and chronic hepatitis C infection. Therapy with a variety of specific agents was discussed as well as the general approach to aggressive therapy and favorable factors for initiating this approach. Unfortunately, no effective therapy is available for rabies at this time. However, until recently only patients who received rabies vaccine prior to the onset of their clinical disease have survived (3). There was a recent American survivor who did not receive rabies vaccine and was the subject of a case report (4), but the reasons for her recovery remain unexplained and controversial.

A number of approaches for treating rabies have been unsuccessful in the past. Therapy with human leukocyte interferon, given as high-dose intraventricular and systemic (intramuscular) administration, in three patients was not associated with a beneficial clinical effect, but this therapy was not initiated until between 8 and 14 days after the onset of symptoms (5). Similarly, antiviral therapy with intravenous ribavirin (16 patients given doses of 16-400 mg) was unsuccessful in China (6). An open trial of therapy with combined intravenous and intrathecal administration of either ribavirin (one patient) or interferon-α (three patients) was also unsuccessful (7). Anti-rabies virus hyperimmune serum of either human or equine origin has been administered intravenously and by the intrathecal routes, but there was no beneficial effect (8-11).

In 2004 a 15-year-old female survived rabies in Wisconsin (4). She was bitten by a bat, which escaped and she failed to receive appropriate post-exposure rabies prophylaxis. About one month later she presented with typical clinical features of rabies. The cornerstone of her therapy was therapeutic (induced) coma, which consisted of intravenous benzodiazepines (midazolam) with supplemental barbiturates (phenobarbital) administered in order to maintain a burst-suppression pattern on her electroencephalogram. In addition, she was given intravenous ketamine, intravenous ribavirin, and amantadine. Ribavirin has antiviral activity against rabies virus; amantadine was the subject of only a single previous in vitro report in rabies virus infection (12). On presentation the patient had neutralizing anti-rabies virus antibodies. She has made a fairly good neurological recovery (13). The unanswered question is whether any of the specific therapy she received, apart from good supportive care in a critical care setting, played a fundamental role in her favorable outcome. Dr. Rodney Willoughby tirelessly promotes and champions this approach to the therapy of human rabies, which has been deemed the “Milwaukee Protocol.”

What viral factors may have been important for the girl’s recovery? The bat rabies virus variant was not isolated and may have had attenuated biological properties (14). It is likely that bat rabies virus strains may be less virulent than canine rabies virus strains that are responsible for most
human cases of rabies. A previous survivor, who received rabies vaccine prior to the onset of disease, was also infected with a bat rabies virus variant and made an excellent recovery (15). There are preliminary reports of another similar survivor (16), who, likely incidentally, also received the Milwaukee Protocol. Often diagnostic tests, including detection of rabies RNA using the reverse transcription – polymerase chain reaction (RT-PCR) technique and detection of rabies virus antigen using the direct fluorescent antibody technique on tissues and/or fluids (brain tissues not tested), are usually negative in rabies survivors, even in cases where immunization occurred prior to the onset of disease. This is likely because there is immunologically – mediated viral clearance, which is essential for recovery in experimental studies. The Wisconsin girl had developed neutralizing anti-rabies virus antibodies at the time of admission to hospital, which probably occurs in less than 20% of rabies patients. The presence of neutralizing anti-rabies virus antibodies is a marker of an active adaptive immune response that is essential for viral clearance (17). There have been six survivors of rabies who received rabies vaccine prior to the onset of their disease and only one survivor who had not received vaccine. This supports the notion that an early immune response is associated with a positive outcome.

Why is therapy using therapeutic (induced) coma not a good idea? First of all, what is the scientific rationale for therapeutic coma? There is really none at all, and this was pointed out in the Editorial accompanying the case report (18). Therapeutic coma suggested for the therapy of rabies is not just sedation. Therapeutic coma is the deliberate depression of the level of consciousness to reach a burst – suppression pattern on the electroencephalogram, which has been used, although there is doubt if this degree of suppression of brain function is absolutely necessary (19,20), for the management of status epilepticus. Status epilepticus is a neurological emergency that has important life threatening consequences that include systemic failure and permanent neurological injury that is thought to be related to a metabolic-substrate mismatch (20-22). In addition to lacking scientific rationale, there is no experimental evidence supporting this approach for the therapy of rabies or any other infectious disease. Therapeutic coma is not a benign therapy. The therapy itself is associated with many potentially serious adverse effects (20).

Ketamine therapy is another element of the Milwaukee Protocol. When we made recommendations about promising therapies for rabies in 2003, we included intravenous therapy with ketamine (2). This recommendation was based on previous in vitro (23,24) and in vivo (24) studies in rats from Institut Pasteur in Paris, which were published in the early 1990s. Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) antagonist, which was included in the Milwaukee Protocol and administered at a dosage of 48 mg/kg/day as a continuous infusion. The reported in vitro antiviral activity of ketamine was observed at mM concentrations rather than µM concentrations that are associated with activity with NMDA receptors, suggesting an alternative mechanism of action. It has been postulated that ketamine might work through anti-excitotoxic mechanisms, but there is no evidence of excitotoxicity in studies performed in vitro in primary neurons and in an experimental model of rabies in mice at the same dosage that was previously used in rats (25). Furthermore, there was no evidence found supporting a neuroprotective action of ketamine either in vitro or in vivo (25). Even where there is strong experimental evidence of excitotoxicity in animal models, multiple clinical trials in humans have shown a lack of efficacy of neuroprotective agents in stroke (26,27). Hence, it is highly questionable that a strong neuroprotective effect of a therapy given to a single patient without a clear scientific rationale was responsible for a favorable outcome. It is much more probable that this patient would have recovered with only supportive therapy and did well to tolerate the additional “insult” of therapeutic coma without developing significant adverse effects.

It has been claimed that patients receiving the Milwaukee Protocol have survived longer than patients who have not received this therapeutic approach (28). This is not a fair comparison because
extraordinary efforts were made in some cases (e.g., an elderly Canadian patient) to maintain therapy
despite a prolonged absence of brain function, whereas palliation was likely initiated much earlier in
the comparative group that did not receive the Milwaukee Protocol. In the Canadian case, a complete
absence of cortical neurons was observed at autopsy with infection of brainstem and cerebellar
neurons demonstrated with routine histological staining (presence of Negri bodies) and with positive
direct fluorescent antibody staining (29). This should not be considered a therapeutic advance.

Altogether I am aware of at least 14 cases, including 12 summarized in a recent review, in which the
main components of the Milwaukee Protocol have been used and fatal outcomes have resulted (30-
32). There is also evidence that this protocol has been used in additional cases (31), and perhaps
many others, but the details are not known and may never be reported.

Although it remains unclear why an American girl survived rabies in 2004, this outcome offers hope
that aggressive approaches to therapy may become more successful in the future. Unfortunately,
no effective therapy for rabies is available at this time. It remains highly doubtful that the Milwaukee
Protocol will prove to be useful in the management of human rabies. Unfortunately, promotion and
repetition of this therapy may impede progress in developing new effective therapies for rabies. An
improved understanding of basic mechanisms underlying the pathogenesis of rabies in humans and
animals may be helpful in the future design of novel therapies for this ancient disease. This may allow
the development of new therapeutic approaches for the management of this ancient disease.

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