Title: THE MILWAUKEE PROTOCOL - HOPE DOES NOT SUCCEED IN SAVING RABIES VICTIM

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Keywords

Milwaukee protocol, Rabies victim, Success and Failure

Abstract

Rabies is caused by the rabies virus, an RNA based virus of the genus Lyssavirusm transmission typically occurs when virus laden saliva from a rabid animal enters a wound or mucuous membrane. The Milwaukee protocol a novel procedure in which a the patient was placed in a drug induced coma and given an antiviral cocktail composed of ketamine, ribavirus an damantadine. Considering the theory that rabies pathology stems from central nervous system neurotransmitter dysfunction, doctors hypotized suppressed brain activity would minimize damage while the patients immune system developed an adequate response.

Case Report

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Agarwal Anil K[1]

ABSTRACT

Rabies is caused by the rabies virus, an RNA-based virus of the genus Lyssavirus. Transmission typically occurs when virus-laden saliva from a rabid animal enters a wound or mucous membrane. The Milwaukee protocol a novel procedure in which the patient was placed in a drug-induced coma and given an antiviral cocktail composed of ketamine, ribavirin, and amantadine. Considering the theory that rabies pathology stems from central nervous system neurotransmitter dysfunction, doctors hypothesized suppressed brain activity would minimize damage while the patient's immune system developed an adequate response

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INTRODUCTION

The Milwaukee protocol [MP], a procedure reported to prevent death after the onset of rabies symptoms, has been performed over 26 times since its inception in 2004 but has only saved one life. Overwhelming failure has lead health officials to label the protocol a red herring.[1,2]

Rabies is caused by the rabies virus, an RNA-based virus of the genus Lyssavirus. Transmission typically occurs when virus-laden saliva from a rabid animal enters a wound or mucous membrane. Infection typically occurs from a rabid animal bite. The virus travels along peripheral nerves until it reaches the brain and salivary glands. A characteristic rabies symptom is aversive behavior toward water or water consumption called hydrophobia. Individuals demonstrating hydrophobia will generally avoid water and resist drinking it. Other symptoms include anxiety, nerve pain, and itching, impaired sensation of touch, convulsions, paralysis, and coma. Cases among unvaccinated individuals almost always result in death.

The Milwaukee protocol was conceived in 2004 by a team of medical professionals, led by Dr. Rodney Willoughby, after a 15-year-old girl was admitted to a Milwaukee hospital after a rabies diagnosis. After consulting with researchers at the Centers for Disease Control and Prevention in Atlanta, the team formulated and implemented a novel procedure. The patient was placed in a drug-induced coma and given an antiviral cocktail composed of ketamine, ribavirin, and amantadine. Considering the theory that rabies pathology stems from central nervous system neurotransmitter dysfunction, doctors hypothesized suppressed brain activity would minimize damage while the patient's immune system developed an adequate response[3,4].

The patient was discharged from the hospital 76 days after admission. She demonstrated speech impediment and difficulty walking during a clinic visit 131 days after discharge. It is unclear how long those conditions persisted. In subsequent years, the patient attended college. She remains the only Milwaukee protocol [MP] success[4].

There has been confusion regarding the efficacy of the Milwaukee protocol[1].

PRESENTING CONCERN

We report the treatment of a child with rabies, who received the timeliest and complete

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application of the original MP to date, and compare this case with other MP attempts, discussing implications for advancement in the field.

In Jan 2016, a 10 year-old male from the Morena India presented to the Intensive emergency unit of our J.A. Group of Hospital Gwalior 30 km far from Morena with symptoms suggestive of furious rabies. Six months earlier, the patient had been bitten by a dog in the Morena and did not receive rabies vaccine or other post-exposure prophylaxis (PEP); Clinical presentations were sore throat, fever, and fatigue, and they were followed by progressive shortness of breath, dysphasia, and insomnia. In IEU he developed irregular mouth movements, visual hallucinations, agitation, aerophobia, and hypersalivation on second day. Marked heart rate and blood pressure variability were compatible with severe dysautonomia. He was intubated for airway protection. Following thiopental for sedation, he became severely bradycardic, requiring brief cardiopulmonary resuscitation (CPR). Neuromuscular blockade was administered because of pharyngeal and diaphragmatic spasms. Coma was induced with ketamine and midazolam infusions, as recommended in the MP (version 1.1)[1], for presumed rabies.

DIAGNOSTIC FOCUS AND ASSESSMENT

Upon diagnosis of rabies, and after discussion with medicine expert and pediatrician with prior permission of ethical committee & superintendent of JA Group of Hospitals & G.R.Medical College, Gwalior intravenous ribavirin and enteral amantidine, tetrahydrobiopterin (BH4), coenzyme Q10, and ascorbic acid were initiated. With therapeutic coma, dysautonomia steadily improved. Given concerns for development of cerebral electrical silence, vasospasm, and edema, intense neurologic monitoring was initiated. This included continuous electroencephalogram (EEG), continuous cerebral regional oxygen saturation measurement by near-infrared spectroscopy (NIRS), and daily transcranial Doppler (TCD). After all efforts were made, similar to the original MP patient, this victim could not survive on 4th day of admission and succumbed to rabies. Of all MP cases reported to date, our management most closely mirrors that of the index MP case, given the early diagnosis and initiation of therapy, avoidance of immunizations, and direct co management with the MP PI[1].

FOLLOW-UP AND OUTCOMES.

In our case, ongoing viral effects with associated devastating brain injury were observed. This questions the premise that intensive supportive care allows the immune response to clear the virus, while retaining reversibility of neurologic disease. Through 2008, of the 7 reported rabies survivors to hospital discharge[2], only the index MP case did not receive PEP. Rabies virus was detected in 1 case[5]; all others were diagnosed by rabies antibody. More recently, abortive rabies was described in an adolescent female who developed neurologic symptoms after bat exposure and had high rabies antibody titer, without isolation of rabies virus[6]. She survived without ICU care, receiving both active and passive immunization only after a late diagnosis; this and the index MP case were both infected with bat rabies[2,6]. Genetic variability in the host and virus likely contribute to survival. Indeed, there are reports of animals surviving rabies without therapy[7]. Thus, application of the MP may be more successful in specific subgroups of patients.

DISCUSSION

As one of the oldest and deadliest infectious diseases, rabies is long overdue for development of a successful treatment. Six years ago, when the first rabies survivor (without PEP) was described, there was new hope for rabies victims. Unfortunately, subsequent cases illustrate the uncertainties surrounding rabies management and the tremendous resources expended in aggressive supportive care[8]. This case, when taken together with other MP cases to date, suggests that an early immune response may be better correlated with survival, the efficacy of MP antiviral activity is unclear, and ribavirin itself may be immuno

suppressive. Aggressive supportive care has resulted in longer survival times and consequently a wealth of clinical and laboratory data, helping to better understand the natural history of rabies and develop specific questions regarding its patho physiology. Animal models are urgently needed to address these questions, which may ultimately lead to successful outcomes in rabies.

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