Failure of the Milwaukee Protocol in a Child With Rabies

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Rabies has the highest case-fatality rate of all infectious diseases, with 50,000 cases occurring annually worldwide. In 2004 an unvaccinated adolescent survived after novel therapy. We report the management of a child with rabies. Although the implementation of this same therapeutic protocol was successful, the child died after 1 month of hospitalization.

Rabies encephalitis was considered universally fatal in humans until 2004, when an unvaccinated adolescent survived with novel therapy now dubbed the Milwaukee Protocol (MP) [1]. This protocol includes therapeutic coma, antiviral therapy, cerebral vasospasm management, and avoidance of immunization. We report the treatment of a child with rabies, who received the most timely and complete application of the original MP to date, and compare this case with other MP attempts, discussing implications for advancement in the field.

CASE REPORT

In November 2006, an 11 year-old male from the Philippines presented to a community emergency department (ED) with symptoms suggestive of furious rabies. Two years earlier, the patient had been bitten by a dog in the Philippines and did not receive rabies vaccine or other post-exposure prophylaxis (PEP); clinical presentation has been reported elsewhere [2]. Briefly, sore throat, fever, and fatigue were followed by progressive shortness of breath, dysphagia, and insomnia. In the ED, he developed irregular mouth movements, visual hallucinations, agitation, aerophobia, and hypersalivation.

Upon transfer to our children’s hospital ED, mental status alternated between extreme agitation and obtundation. 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.

On admission to the intensive care unit (ICU), simultaneous severe variable hypertension and heart rate suggested neurally mediated catecholamine storm. Echocardiogram revealed severe secondary left ventricular dysfunction. With a fosphenytoin load the patient sustained a second brief bradycardic event, which again responded to CPR. Inotropic support was required for 4 days. Coma was induced with ketamine and midazolam infusions, as recommended in the MP (version 1.1), for presumed rabies.

On hospital day 1 (HD1), direct fluorescent antibody (DFA) detected rabies virus antigen in corneal impressions; serum and cerebrospinal fluid (CSF) serologies were negative. From a saliva sample on HD3, molecular testing performed at the Centers for Disease Control and Prevention (CDC) detected rabies virus RNA, corresponding genetically to Philippine dog rabies. Antibodies immunoglobulin G (IgG) was first detected via indirect immunofluorescence in serum and CSF on HD11 and HD13, respectively. Initial nuchal biopsy was positive by DFA on HD3 and again on HD19.

On HD1, upon diagnosis of rabies, and after discussion with the California Department of Public Health, CDC, and authors of the MP, intravenous ribavirin and enteral amantidine, tetrahydrobiopterin (BH4), coenzyme Q10, and ascorbic acid were initiated. All subsequent titrations and modifications of the MP were made in direct consultation with the MP primary investigator (PI).

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

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by near-infrared spectroscopy (NIRS), and daily transcranial Doppler (TCD).

Cerebral vasospasm was suggested by TCD on HD6 and HD10–HD12, as reported elsewhere [3]; vasospasm-targeted therapies included escalating doses of BH4, followed by milrinone and L-arginine. Serial EEG revealed slowing, progressing to burst suppression by HD13; anticonvulsant prophylaxis included fosphenytoin, midazolam, and phenobarbital. On HD15, pupils became fixed and dilated. Prolonged electrographic seizures developed on HD17. On HD21 topiramate was administered for multifocal spikes; subsequently, the EEG became isoelectric. Medications potentially responsible for this finding were weaned.Computed tomography on HD24 revealed severe cerebral edema; prior neuroimaging, including CT on HD1 and HD13, along with magnetic resonance imaging on HD6 and HD12, was normal. Right frontal lobe biopsy on HD25 showed perivascular cuffing with lymphocytes extending into the surrounding brain and associated microglia, consistent with encephalitis. Support was withdrawn on HD27.

The hospital course included multiple secondary complications previously described in rabies: transient hyponatremia, hemidiaphragmatic paralysis, pancreatitis, hypothyroidism, and heart block requiring transvenous pacing. Additional complications included ventilator-associated pneumonia and peripheral thrombophlebitis. Hospitalization charges exceeded $700,000.

Autopsy revealed an edematous brain, with diffuse lymphocytic encephalitis and widespread loss of neurons in the cortex, with many residual neurons undergoing necrosis. The cerebellum demonstrated extensive loss of Purkinje cells and internal granule cell neurons. Negri bodies were identified (Figure 1). Scattered microinfarcts and small perivascular hemorrhages were also seen, possibly representing a component of vasospasm and associated thromboembolism. Overall, pathology showed evidence of severe lymphocytic encephalitis with superimposed secondary hypoxic ischemic encephalopathy. CDC confirmed the presence of rabies particles in brain tissue by DFA and molecular studies.

**DISCUSSION**

Rabies encephalitis is almost universally fatal, and therapy has been classically palliative. Prior to 2004, there were only 5 documented human survivors, all of whom had received PEP, albeit incomplete or late [4]. In 2004, after a novel protocol was applied (MP), the first survival without PEP was reported [1]. Since then, the MP has been viewed as a potentially effective therapy.

As reported to date in the MP Rabies Registry, variations of the MP have been applied to 25 additional patients, with 3 minimally documented “survivors” [5]. A girl from Colombia [6] and a man from Peru died (HD76 and HD70, respectively) after presumed viral clearance and discharge from the ICU, from nonrabies attributable medical complications (R. E. Willoughby, personal communication, 2011). The third survivor, a Brazilian boy with bat rabies [7] who received partial PEP before onset of symptoms, is living at home. 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 comanagement with the MP PI.

The MP has evolved and is currently in version 3.1 [5]. Its original assumptions, however, remain unchanged. First, wild-type rabies infection confers little viral or immune-mediated cytopathic effect and is therefore theoretically reversible. Second, a natural immune response is sufficient to clear the virus. Third, BH4 deficiency and generalized cerebral vasospasm may be in the causal pathway of rabies mortality. Four general principles guide therapy: (1) prolonged therapeutic coma to prevent early life-threatening dysautonomia; (2) antiviral therapy; (3) prophylaxis, monitoring, and treatment of cerebral vasospasm; and (4) avoidance of immune prophylaxis. Of these principles, only the first has been used consistently with success.

Unfortunately, antiviral therapy with combined ribavirin, ketamine, and amantadine has not shown antiviral effect in MP patients [5]. Additionally, ribavirin may delay the antibody response and is no longer recommended [8]. Conversely, given its favorable side effect profile, amantadine is still recommended.

Similarly, management of cerebral vasospasm has shown little benefit [4]. Although suggested by TCD, confirmatory imaging was not performed, and autopsy did not show evidence of major vasospasm. The MP has used multiple vasodilator agents, but none appear to have prevented brain injury [4].

The rabies antibody response typically appears by 2 weeks. The MP postulates that a vigorous immune response may exacerbate the disease process [5], and it avoids active immunization.

**Figure 1.** Negri body (arrow) is identified within a Purkinje cell. Photomicrograph of the cerebellum (hematoxylin-eosin stain; original magnification \(\times 400\)).
Once symptoms develop. Of note, the Brazilian survivor [7] received 4 of 5 recommended PEP vaccinations before symptoms. Furthermore, the index survivor, in whom rabies virus was never detected, had antibodies at 1 week [1]. The MP also avoids passive immunization with rabies immune globulin (RIG) because of theoretical interference with the native immune response and unclear CNS penetration. However, RIG may have a protective role in the heart and other organs, where rabies virus has been demonstrated [9].

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 [1, 4, 7], only the index MP case did not receive PEP. Rabies virus was detected in 1 case [7]; 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 [10]. 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 [1, 10]. Genetic variabilities in the host and virus likely contribute to survival. Indeed, there are reports of animals surviving rabies without therapy [11]. Thus, application of the MP may be more successful in specific subgroups of patients.

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 [12]. 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 immunosuppressive. 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 pathophysiology. Animal models are urgently needed to address these questions, which may ultimately lead to successful outcomes in rabies.

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