Critical Appraisal of the Milwaukee Protocol for Rabies: This Failed Approach Should Be Abandoned

Frederick A. Zeiler, Alan C. Jackson

ABSTRACT: The Milwaukee protocol has been attributed to survival in rabies encephalitis despite a lack of scientific evidence supporting its therapeutic measures. We have reviewed the literature with reference to specific treatment recommendations made within the protocol. Current literature fails to support an important role for excitotoxicity and cerebral vasospasm in rabies encephalitis. Therapies suggested in the Milwaukee protocol include therapeutic coma, ketamine infusion, amantadine, and the screening/prophylaxis/management of cerebral vasospasm. None of these therapies can be substantiated in rabies or other forms of acute viral encephalitis. Serious concerns over the current protocol recommendations are warranted. The recommendations made by the Milwaukee protocol warrant serious reconsideration before any future use of this failed protocol.

RÉSUMÉ: Évaluation critique du protocole de Milwaukee pour le traitement de la rage: cette approche inefficace devrait être abandonnée. La survie dans l’encéphalite rabique a été attribuée au protocole de Milwaukee malgré l’absence de données scientifiques à l’appui. Nous avons revu la littérature traitant des recommandations spécifiques de traitement faites dans le cadre de ce protocole. Aucune donnée de la littérature actuelle ne supporte que l’excitotoxicité et le vasospasme cérébral jouent un rôle important dans l’encéphalite rabique. Les traitements suggérés dans le protocole de Milwaukee incluent le coma thérapeutique, l’infusion de kétamine, l’amantadine et le dépistage, la prévention et le traitement du vasospasme cérébral. Il n’existe aucune preuve que de ces traitements soient efficaces contre la rage ou toute autre forme d’encéphalite virale aigüe. Il est donc justifié d’entretenir de graves réserves au sujet des recommandations contenues dans le protocole actuel. Les recommandations contenues dans le protocole de Milwaukee méritent d’être reconsidérées dans leur ensemble avant toute utilisation future du protocole actuel qui s’est avéré inefficace.

Keywords: critical care, infectious diseases, infections of the nervous system, intensive care, virology, Milwaukee protocol, neuroprotection, rabies, therapy

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Rabies encephalomyelitis remains a difficult therapeutic challenge. To date, numerous therapies have been implemented with all failing to show therapeutic efficacy.1,2 Few reports of survivors exist in the literature, with the majority of survivors having received post-exposure prophylaxis with one or more doses of rabies vaccine.3 Documented survivors of rabies may, at least in part, represent advances in cardio-respiratory and other supports within modern critical care units and not be related to specific rabies directed therapies.

In 2004 a young patient from Wisconsin survived rabies and her therapy has been dubbed the Milwaukee protocol and relentlessly promoted.4 The Milwaukee protocol is a treatment regimen for rabies focused on therapeutic coma and the use of N-methyl D-aspartate (NMDA) receptor antagonist therapy. This protocol has received attention after recovery with mild neurological deficits of one patient who did not receive any rabies vaccine.4,5 Since the case report was published in 2005,4 many changes have been made in the protocol to arrive at its current rendition.6

Critics of the Milwaukee protocol raise concerns of the regimen’s lack of efficacy in human rabies, with at least 31 documented failures reported in the literature to date (Table 1). There are claims that patients from Colombia19,20 and Peru12 who died are survivors because they survived the initial phase of acute illness. Another survivor probably did not have rabies,39 whereas others received doses of rabies vaccine prior to the onset of their disease40 similar to rabies survivors who did not receive the Milwaukee protocol. Given the concerns with the Milwaukee protocol, we elected to perform a critical appraisal of the suggested critical care directed therapies within the current protocol version, with a focus on NMDA receptor antagonism, therapeutic coma, and cerebral vasospasm.

We reviewed the available literature regarding the treatment of human rabies encephalitis over the last decade and have summarized all known patients treated with the Milwaukee protocol to date. Furthermore, in order to outline any available evidence to support its use, we reviewed the literature surrounding the Milwaukee protocol for rabies encephalitis. Within the protocol we identified areas of concern for lack of scientific merit. These areas included therapeutic coma, NMDA receptor antagonism, and cerebral vasospasm prophylaxis/detection/treatment.

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METHOD

Search strategy

We performed a review of the literature looking for therapy of all cases of human rabies published from 2005 (the inception of the protocol) to August 2015. MEDLINE, BIOSIS, EMBASE, Global Health, SCOPUS, and Cochrane Library from January 2005 to August 2015 were searched, using individualized search strategies for each database. Finally, reference lists of any review articles or cases on the management of human rabies were reviewed for relevant reports missed. Inclusion criteria were human subjects with rabies encephalitis, prospective or retrospective studies, any study size, and any language. Exclusion criteria were animal studies.

Study selection

A two-step review of all articles returned by our search strategies was performed. First, all titles and abstracts of the returned articles were screened to decide if they met the inclusion criteria. Second, the full text of the chosen articles was then assessed to confirm if they met the inclusion criteria.

Table 1: Cases of human rabies with treatment failures that used the main components of the Milwaukee protocol. (Updated with permission from Jackson AC: Therapy in human disease, in Rabies: scientific basis of the disease and its management, Third Edition, edited by AC Jackson, 2013, Elsevier Academic Press, Oxford, UK, pp 573-587; Copyright Elsevier

<table>
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*Personal communication from Dr. Rita Medeiros, University of Para, Belem, Brazil.

**Patient was initially in a vegetative state but died within six months while in hospice care (Personal communication, Dr. Ya-Sung Yang, Tri-Service General Hospital, Taipei, Taiwan).
Data collection

Data fields included patient demographics, region of origin, and outcome. We also documented the use of therapeutic coma, ketamine, amantadine, and ribavarin. Any cases describing the use of the main components of the Milwaukee protocol were added to the data from a previously published table from 2013.3 This was tabulated in Table 1. Of note, all 31 patients have died as a result of their illness due to rabies, including complications and related to neurological sequelae.

RESULTS

The data from all patients from United States/Canada/United Kingdom treated for rabies encephalitis from January 2005 to December 2014 are summarized in Table 2.

Table 2: Therapy in all 29 cases of human rabies occurring in the United States, Canada, and United Kingdom during the period 2005-2014. Twelve cases (41%) received major components of the Milwaukee protocol (therapeutic coma and ketamine). Therapy failed in all; the only survivor (Case No. 14) did not have neutralizing anti-rabies virus antibodies and likely did not have rabies, similar to Case No. 8, who did not receive any specific therapy and did not require critical care.41

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*Two patients recovered from an illness without the presence of neutralizing anti-rabies virus antibodies, raising very serious doubts about a diagnosis of rabies.

**Personal communication, Jesse Blanton, Center for Disease Control and Prevention, Atlanta, GA, USA.
Phenobarbital was used to maintain a burst-suppression pattern on the electroencephalogram for therapeutic coma for the index case.4

Both the TBI and stroke literature have displayed some benefit to NMDA receptor antagonism in animal models, but no randomized trial in TBI has showed some benefit to functional outcome when administered within 4 to 16 weeks of injury.63

Cerebral vasospasm recommendations

- Nimodipine prophylaxis: Reduces vasospasm rates, merits serious reconsideration.
- Supplement vitamin C and sapropterin: Reduces vasospasm rates, merits serious reconsideration.
- TCD monitoring during first two weeks: Monitor for signs of vasospasm, merits serious reconsideration.

NMDA Receptor Antagonism

- Amantadine (also ketamine (see above)): Antiviral agent; NMDA receptor antagonism, merits serious reconsideration.

Antiviral recommendations

- Ritonavir and amantadine: Antiviral agent; NMDA receptor antagonism, merits serious reconsideration.

Cerebrospinal fluid analysis

- Evaluate cerebrospinal fluid (CSF) for rabies virus antibodies, raising serious doubts about whether these individuals actually had rabies encephalitis.
- These cases the patients failed to develop neutralizing anti-rabies virus antibodies, raising serious doubts about whether these individuals actually had rabies encephalitis.

No rabies vaccine or rabies immunoglobulin

- Potentially decreased survival due to impaired antibody production, controversial, but beyond the scope of this review.

Maintain isolation

- Prevent exposures to health care workers and visitors.

Transfer to tertiary care center

- For critical care management and monitoring.

Gain central access and start enteral feeds

- Usual ICU protocol for expected long term ICU stay.

Maintain euglycemia, euthermia, euvolemia, euonatremia, and eucarbia

- Maintain homeostasis.

DVT prophylaxis

- Patients immobile for long periods.

Therapeutic coma

- Therapeutic coma for first week: To reduce mortality related to autonomic instability, merits serious reconsideration.
- Use ketamine as a sedative: Achieve sedation and NMDA receptor antagonism, merits serious reconsideration.
- Consider benzodiazepines: “minimizes vascular reactivity” during suctioning and turning.
- Avoid propofol: Causes “over sedation”.
- Avoid barbiturates*: Immunosuppressant.

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- Supplement vitamin C and sapropterin: Reduces vasospasm rates, merits serious reconsideration.
- TCD monitoring during first two weeks: Monitor for signs of vasospasm, merits serious reconsideration.

Table 3: Summary of the Main Components of the Milwaukee Protocol, version 4.06

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Rationale</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No rabies vaccine or rabies immunoglobulin</td>
<td>Potentially decreased survival due to impaired antibody production</td>
<td>controversial, but beyond the scope of this review</td>
</tr>
<tr>
<td>Maintain isolation</td>
<td>Prevent exposures to health care workers and visitors</td>
<td></td>
</tr>
<tr>
<td>Transfer to tertiary care center</td>
<td>For critical care management and monitoring</td>
<td></td>
</tr>
<tr>
<td>Gain central access and start enteral feeds</td>
<td>Usual ICU protocol for expected long term ICU stay</td>
<td></td>
</tr>
<tr>
<td>Maintain euglycemia, euthermia, euvolemia, euonatremia, and eucarbia</td>
<td>Maintain homeostasis</td>
<td></td>
</tr>
<tr>
<td>DVT prophylaxis</td>
<td>Patients immobile for long periods</td>
<td></td>
</tr>
<tr>
<td>Therapeutic coma</td>
<td>To reduce mortality related to autonomic instability</td>
<td>merits serious reconsideration</td>
</tr>
<tr>
<td>Use ketamine as a sedative</td>
<td>Achieve sedation and NMDA receptor antagonism</td>
<td>merits serious reconsideration</td>
</tr>
<tr>
<td>Consider benzodiazepines</td>
<td>“minimizes vascular reactivity” during suctioning and turning</td>
<td></td>
</tr>
<tr>
<td>Avoid propofol</td>
<td>Causes “over sedation”</td>
<td></td>
</tr>
<tr>
<td>Avoid barbiturates*</td>
<td>Immunosuppressant</td>
<td></td>
</tr>
<tr>
<td>NMDA Receptor antagonism</td>
<td>Amantadine (also ketamine (see above)): Antiviral agent; NMDA receptor antagonism</td>
<td>merits serious reconsideration</td>
</tr>
<tr>
<td>Cerebral vasospasm recommendations</td>
<td>Nimodipine prophylaxis: Reduces vasospasm rates</td>
<td>merits serious reconsideration</td>
</tr>
<tr>
<td></td>
<td>Supplement vitamin C and sapropterin: Reduces vasospasm rates</td>
<td>merits serious reconsideration</td>
</tr>
<tr>
<td></td>
<td>TCD monitoring during first two weeks: Monitor for signs of vasospasm</td>
<td>merits serious reconsideration</td>
</tr>
</tbody>
</table>

IMC = intensive care unit, DVT = deep vein thrombosis, NMDA = N-methyl d-aspartate, TCD = transcranial dopplers.

*Phenobarbital was used for maintain a burst-suppression pattern on the electroencephalogram for therapeutic coma for the index case.4

A total of 29 patients with rabies encephalitis were treated during the described period. Only two patients treated during this period have been reported as survivors.39,41 However, in both of these cases the patients failed to develop neutralizing anti-rabies virus antibodies, raising serious doubts about whether these individuals actually had rabies encephalitis.

Appraisal of the Milwaukee Protocol

The current version of the Milwaukee protocol for the treatment of rabies viral encephalitis can be accessed online.6 Table 3 summarizes the main components of the protocol.

NMDA Receptor Antagonism

Glutamate, the major stimulatory neurotransmitter in the central nervous system, mediates stimulation of NMDA receptors leading to neuronal calcium uptake, intracellular acidosis, nitric oxide synthase (NOS) mediated free radical formation, and mitochondrial dysfunction, which cause neuronal injury and death.59 Concerns over glutamate mediated excitotoxic neuronal damage have been raised.64 To no surprise NMDA receptor antagonists have been employed in both animal models,65 and human subjects.66 In Sindbis virus encephalomyelitis64,67,68 and human immunodeficiency virus infection,69 there is established experimental evidence supporting excitotoxicity. However, this is lacking in rabies and in an animal model there is a lack of efficacy of ketamine therapy,70 which argues against this hypothesis. To date evidence for glutamate mediated excitotoxic neuronal damage in viral encephalitis is suggested in some animal models, and the implementation of NMDA receptor antagonists in human viral encephalitis is experimental. In corollary, literature is emerging suggesting that complete blockade of the NMDA receptor may have consequences on the normal inflammatory cascade and affect clearance mechanisms in bacterial infections, leading to impaired defense mechanisms.71 This concern has yet to be confirmed in viral illnesses.

Milwaukee Protocol Recommendations

Within the current version of the Milwaukee protocol, reference to the use of NMDA receptor antagonists has been made due to speculation about a role of NMDA receptor mediated excitotoxicity and also their potential antiviral properties. Therapy with both ketamine and amantadine has been recommended.
Ketamine is a non-selective NMDA receptor antagonist that has been investigated for its antiviral properties in animal models of rabies. Ketamine has not been shown to be an effective neuroprotective agent in any neurological illness. Furthermore, outside of selected case reports, ketamine has not been studied as a therapy for autonomic instability.

Amantadine’s antiviral effects in rabies virus infection are based on limited in vitro studies and it failed to show efficacy in mice when inoculated into the site of intramuscular inoculation of wild-type rabies virus at daily intervals; it has not been evaluated in experimental rabies or in human rabies. Believed to inhibit rabies virus production, the current data suggest that amantadine likely does not impair viral attachment and penetration. Thus, the role for amantadine as an antiviral agent in rabies is unclear and it cannot be recommended at this time. Similarly, the neuroprotective role of amantadine to date has been only demonstrated in the TBI literature. No data exists to suggest its efficacy in human viral encephalitis.

Given the failure of NMDA receptor antagonist therapy for neuroprotection in a variety of neurological disorders, the lack of evidence supporting its antiviral and neuroprotective properties in rabies and other forms of viral encephalitis, rabies models questioning a pathogenetic role of excitotoxicity, and a lack of evidence supporting the use of NMDA receptor antagonist therapy for autonomic instability, the current recommendations for ketamine or amantadine therapy within the Milwaukee protocol cannot be supported.

Cerebral Vasospasm

Pathophysiology

Cerebral vasospasm leading to delayed cerebral ischemia (DCI) is commonly described in the literature following aneurysmal subarachnoid hemorrhage (SAH) and in TBI. Thus, the majority of literature on monitoring and therapies for DCI secondary to cerebral vasospasm is based on data from these populations. Cerebral vasospasm has not been generally recognized in viral encephalitis and there is no clinical or pathological evidence supporting its occurrence in this setting, including in rabies.

Currently, few cases of imaging/radiographic cerebral vasospasm in rabies have been described. There have not been any cases of symptomatic DCI secondary to cerebral vasospasm reported in human rabies. Mechanistically, cerebral vasospasm in the setting of SAH and TBI is thought to be related to an inflammatory response secondary to blood breakdown products in contact with the vessel adventitia. In addition, the role of microthrombosis, microvascular spasm, and failure of autoregulation in cerebral vasospasm have been questioned.

In rabies this theory of vasospasm does not apply. It is hypothesized that, in rabies, there is a loss of nitric oxide synthase (NOS) function secondary to an induced tetrahydrobiopterin deficiency and this NOS dysfunction, in concert with inflammation, can lead to cerebral vasospasm. This theory has yet to be substantiated. Furthermore, with the lack of human clinical descriptions and neuropathological studies in rabies supporting the presence of cerebral vasospasm, it is unlikely that it plays any important role in rabies encephalitis.
Monitoring

Monitoring of cerebral vasospasm is a contentious topic. Recommendations for regular monitoring via transcranial Doppler (TCD), computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) have been made in the literature. Given the speed and ability to perform at the bedside, TCD monitoring has been recommended as a screening tool for vasospasm in both SAH and TBI. However, there are concerns with inter-/intra-operator variability of the results, limitations in technique due to patient specific cranial windows, and concerns on reliability of readings for non-middle cerebral artery vessels.

The Milwaukee protocol recommends regular TCD monitoring for vasospasm in rabies. Given the current controversy, this strong recommendation cannot be supported. In addition, given the recommendation of an aggressive sedative regimen for rabies patients within the protocol, the utility of screening patients with TCD for vasospasm in this context is questionable because the indication for treatment is based on the presence of clinical examination changes, which may, or may not, represent the features of DCI. In the setting of therapeutic coma, as recommended by the Milwaukee protocol, the treating intensivist’s ability to determine if TCD defined vasospasm is clinically relevant is dramatically impaired.

The Milwaukee protocol defines treatable vasospasm as those patients with either a bilateral increase in TCD based middle cerebral artery (MCA) velocities with normal resistance or a bilateral decrease in MCA velocities with increased resistance. The exact cutoff for “increased” or “decreased” MCA velocities is not described and no reference to standard TCD definitions of cerebral vasospasm in aneurysmal SAH are made. The potential adverse consequences of implementing hypertensive therapy or vasodilator therapy for TCD defined vasospasm in rabies, without recognized clinical consequences, should not be ignored.

In addition to TCD monitoring, the Milwaukee protocol recommends continuous electroencephalogram (cEEG) monitoring for DCI secondary to cerebral vasospasm. It has been suggested that the presence of spreading depolarizations may be an indication of underlying DCI. However, recent literature indicates a lack of large prospective studies utilizing cEEG monitoring in aneurysmal SAH patients, and does not support widespread use of this modality as a monitor for DCI secondary to cerebral vasospasm. Thus, the recommendation of its use in rabies encephalitis as a monitor for DCI is clearly not warranted.

Prophylaxis for Vasospasm

Prophylaxis of vasospasm has also been recommended within the Milwaukee protocol. The use of nimodipine, vitamin C, sapropterin and L-arginine have been recommended within the most recent version of the protocol.

Nimodipine, a calcium channel antagonist, has been widely used in SAH patients as a means of prophylaxis against cerebral vasospasm and is currently considered standard care in this patient population. In the TBI population, where cerebral vasospasm is also prevalent, nimodipine has failed in large trials to have an impact. Hence, the recommendation of nimodipine to prevent rables associated vasospasm is unsubstantiated.

Vitamin C therapy has been investigated as a potential means to prevent cerebral vasospasm in aneurysmal SAH by altering the activity of oxyhemoglobin. This benefit has not been demonstrated in human subjects. Regardless, vitamin C therapy has been included in the protocol. Furthermore, a small reports have eluded to an “antiviral” effect of vitamin C in rabies models. This effect, again, has not been supported in human reports.

Sapropterin supplementation has been suggested, given the concerns of tetrahydrobiopterin deficiency leading to NOS dysfunction and potentiation of cerebral vasospasm. No data exist to suggest that supplementation leads to a decrease in cerebral vasospasm or improvement in outcome.

Finally L-arginine has also been recommended. L-arginine is postulated to induce NOS function and promote vasodilation. The use of L-arginine to prevent or treat cerebral vasospasm has not been supported by the literature, thus its recommended use in the treatment of rables should be cautioned.

Treatment

Currently, the management of cerebral vasospasm, regardless of the underlying neurologic cause, is based on literature from aneurysmal SAH patients. The current “gold standard” therapy for symptomatic DCI post aneurysmal SAH is hypertension therapy, with the goal of raising mean arterial pressures (MAP) in order to preserve cerebral blood flow (CBF) in at risk territories. Previous therapies consisted of hypertension, hypervolemia and hemodilution, termed “Triple-H” therapy.

Treatment of TCD or CTA defined cerebral vasospasm, without a clinical correlate of symptomatic DCI has also been recommended by the Milwaukee protocol. The Milwaukee protocol references “Triple-H” therapy as the treatment for TCD defined vasospasm in rabies encephalitis. This is concerning considering the evidence in the SAH literature warning against hypervolemia and hemodilution therapy.

In addition to triple-H therapy, the Milwaukee protocol recommends continuous intravenous infusions of nicardipine for TCD defined cerebral vasospasm. This is currently not recommended as standard care in any guidelines for the management of cerebral vasospasm. To date, only a small number of studies in aneurysmal SAH have studied nicardipine, displaying an improvement in radiographic vasospasm, without a robust impact on outcome. Its recommendation in rabies is unwarranted.

Overall, the treatment recommendations made by the Milwaukee protocol for cerebral vasospasm in rabies encephalitis are not the current standard care for vasospasm in other neurological disorders and are unwarranted.

Conclusions

Despite initial hope and enthusiasm for the Milwaukee protocol in the treatment of rables, subsequent trials of this regimen have failed. Serious concerns over the current protocol recommendations are warranted in light of a weak scientific rationale. The recommendations for therapeutic coma, NMDA receptor antagonists, and the screening/prophylaxis/treatment of cerebral vasospasm are supported by little to no scientific evidence in the literature. The recommendations made by the protocol warrant serious reconsideration before any future use of this failed protocol. Unfortunately, we do not have an alternative protocol to put forward for therapy of patients with rables. We hope that novel therapies will be developed after we have an improved understanding of rables pathogenesis and further research in good animal models is very important. We have recently published a
detailed review of antiviral therapy in rabies \cite{72} and potential approaches to management,\cite{73} including the possibility of regional (head and neck) cooling (hypothermia).

**Disclosures**

Frederick Zeiler and Alan Jackson do not have anything to disclose.

**References**


