

## Editorial

# Ethics and the “Milwaukee protocol” for human rabies treatment

Rabies has been considered for centuries an inevitably fatal disease. However, several survivors from clinical rabies had been reported without having received specific treatment other than good nursing care and respiratory support [1]. Furthermore, it is well documented that many mammals, including bats, dogs, raccoons, raccoon dogs, skunks, pigs and even the very susceptible fox can survive untreated rabies infection [2-8]. Natural resistance, virulence of the virus, site of the inoculum and viral load are factors influencing susceptibility. It should be no surprise if rabies is not an invariably fatal disease in man as well [9, 10]. There is evidence that virtually asymptomatic, mild, unrecognized, or abortive cases of rabies do occur. One was in a 68 year old Alaskan Eskimo fox trapper who, in a survey by the late Erich Folmann of the University of Alaska, Fairbanks, was found to have a high neutralizing rabies antibody titer. This, without any history of serious illness or prior rabies vaccination [11].

In 2005, a 15 year old American girl was bitten by an insectivorous bat and, without receiving any post-exposure prophylaxis, survived a long and stormy hospital stay and is now a college graduate. She was managed at Milwaukee using induction of deep anesthesia and a series of drugs supposed to counteract excitotoxicity and kill viruses. Experiments in animals do not substantiate the role of excitotoxicity and the benefit of ketamine [12]. Her treatment is now widely known as the “Milwaukee Protocol” (MP) and resulted in several optimistic publications [13-15]. Interest and optimism created by media worldwide, led to attempts to duplicate MP. Several rabies patients were said to have recovered sufficiently to have left the hospital. However, the extent and duration of recovery was not always well documented. One such subject, in Equatorial Guinea, was said to have later died of malnutrition [16]. Among four survivors with good functional outcomes, two had coma induction and one required no intensive care support [9]. There are now at least 21 cases of failure of the MP. Most

have been reported from tertiary care centers and have been well documented [17-23]. Noteworthy is that most were in patients that were infected by bats. This raised the question whether less virulent virus strains had been responsible. A more impressive fact is that survivors managed to have rabies virus neutralizing and non-neutralizing antibodies on, or soon after, presentation and that no virus RNA could be isolated using sophisticated technology throughout their hospital course. This was not so in MP failure cases where viral RNA increased exponentially till death [24-26].

MP with induced deep anesthesia, carries an impressive number of life threatening adverse reactions. These range from shock, extreme hypotension, cardiogenic, and non-cardiogenic pulmonary edema, arrhythmias and disruption of autonomic and endocrine regulatory systems, hepatic and renal failure, and rhabdomyolysis [23]. One experience at King Chulalongkorn Memorial Hospital, Bangkok occupied the near full attention of at least six senior staff for days. They were needed at the ICU to cope with recurrent unexpected complications not previously encountered in conventional ICU care. The later addition of Nimodipine to MP with the notion of counteracting cerebral vasopressor activity, may have intensified circulatory complications. There has been no pathology or neuroimaging evidence substantiating that vasospasm plays a role in rabies encephalitis. The cost of this one case, born by the Thai government, could have been used to provide intradermal preexposure rabies vaccination for approximately 26,000 children in a major Bangkok slum where rabies exposures from stray dogs are an almost daily event [23]. The extensive promotion of the MP in the media and in professional publications, has resulted in persistent use despite many published negative outcomes. The last one (May 2012) was in a 19 year old farmer in South Africa where the MP was applied unsuccessfully [26].

The Milwaukee protocol carries significant risks from complications due to the near total suppression of defense responses. These risks, in a possibly natural survivor, are clearly unjustified. This problem has been extensively and repeatedly discussed among the rabies

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consortium of clinicians and scientists in Bangkok as well as with colleagues abroad. All survivors have shown endogenous mustering of vigorous immune defenses [10, 26]. No viral RNA could be identified in saliva, spinal fluid, skin biopsies or corneal smears on, or soon after, admission to the hospital. Extensive efforts to maintain life are clearly indicated in subjects who are conscious and have an antibody response, particularly in spinal fluid. The care of such a potential survivor must not be compromised by the added risks of applying the MP. Transfer to a tertiary care center of such a patient, where special diagnostics and sophisticated treatment is available, should be encouraged wherever possible. However, all rabies cases require the best available nursing and comfort care [10]. Continuing application of the MP creates false hopes and is scientifically on the fringe of respectability.

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