TOWARDS A PARADIGM SHIFT IN RABIES TREATMENT

Ramkumar Hariharan, PhD, Cancer Research Program, Rajiv Gandhi Center for Biotechnology, Thiruvananthapuram - 695014, Kerala, India. Email: rmhariharan@rgcb.res.in

The almost fairy tale-like story of 15-year old Jeanna Giese, who became a medical first in 2004, by surviving rabies without any post-exposure prophylaxis, has sparked renewed interest and enthusiasm in the treatment of this fatal disease. The completely novel medical protocol that was used to treat Giese was crafted by Dr Rodney Willoughby and his team at the Children’s Hospital in Wisconsin, Milwaukee. Befittingly, this treatment protocol has been dubbed the ‘Milwaukee protocol’ and has since been deployed in several other hospitals to successfully treat five additional cases of clinical rabies till date.

Before we turn to some of the salient features of the Milwaukee protocol, it is worth perusing the history of medicine in order to fully appreciate the importance of this achievement. Rabies or hydrophobia enjoys a singularly dubious honor of having the highest case fatality ratio of any communicable disease. The first landmark in the treatment of rabies was made by the great Louis Pasteur in 1885, when he used a vaccine developed jointly by him and his colleague, Emile Roux, to save a 9-year old boy, Joseph Meister, who had been mauled by a rabid dog. Thereafter, barring a few isolated instances in recorded medical literature, the treatment of rabies has remained literally unchanged- the crucial “message” being that without timely administration of post-exposure vaccine, rabies is invariably fatal once symptoms begin to manifest. The Milwaukee protocol, which is given to patients presenting
with symptoms of clinical rabies and who have not had a course of the prophylactic vaccine or rabies antibodies, indeed does deserve historic if not histrionic attention.

The essence of the Milwaukee protocol is best brought out by briefly recounting the case report of Jeanna Giese. Giese had sustained a small wound in her left index finger during her attempts to rescue and free a bat that had found its way indoors. Approximately a month later, she developed a progression of ominous symptoms that included a tingling in her left hand, generalized fatigue, double vision, and an unsteady gait, gradually followed by blurred vision, nausea and slurred speech. At the Children’s hospital in Milwaukee, the 15-year old was diagnosed with clinical rabies on the second hospital day. Taking into account the grim prognosis of the disease, the physicians who treated her, laid down two alternative courses of action before Giese’s parents: a palliative approach aimed at toning down the morbidity while accepting the inevitable fatality of the disease and an intrepid, never-before-tested aggressive protocol that promised a slim ray of hope for Giese’s survival. The latter proposal seemed more worthy to the parents and was implemented.

The aggressive protocol involved the use of two sets of drugs: (a) ketamine and midazolam, that exert anti-excitotoxic effects on the central nervous system, and (b) ribavirin and amantidine, two antivirals. A combination of these agents was used to achieve a medically induced coma while the patient was placed on life-support by intensive care. Continuous monitoring of the patient’s vital signs along with measurement of serum levels of rabies antibodies served as endpoints for evaluating therapy benefit. Although a multitude of medical
complications did set in, including hemolysis, pancreatitis and partial liver failure, these toxicities were kept under check via administration of apropos and timely medical interventions. Increasing levels of rabies antibody were noted from the eight day, with concomitant resolution of many of the central nervous system symptoms. The triumph of Giese’s removal from isolation after a month and her subsequent discharge from the hospital, cured of the fatal disease, has found its way into countless articles and news clippings worldwide.

The Milwaukee protocol has since undergone minor modifications, but its key tenets remain the same. Specifically, later versions of the protocol have done away with the antiviral drug, ribavirin, since clearance of the virus from the brain seemed to depend solely on the maturation of a native immune response. Further, the absence of any major long term neurologic disabilities or deficits in these rabies survivors serves to bolster the promise of the Milwaukee protocol. Indeed, Jeanna Giease, the first unvaccinated rabies survivor has since then returned to an almost normal life, harboring only minor problems with her speech and gait.

A careful examination of the motivation and rationale behind this novel treatment reveals several ideas that likely have played key roles in its astounding success. Dr Willoughby had taken note of the fact that infection with the rabies virus rarely leads to overt destruction of neural structures; rather, the virus seems to work by perturbing communication within the brain. Secondly, administration of rabies antibodies during the clinical phase leads to an overly heightened immune response culminating in severe brain inflammation. Thirdly, he went ahead based on a bold assumption, extrapolated from studies in animal models: that
the body can clear the rabies virus from the brain given sufficient time. The Milwaukee protocol successfully addressed all these issue by essentially “shutting down” the brain and thereby giving time for the body to mount an immune response to clear the virus. Noteworthy is that unlike contemporary efforts at prolonging survival of rabies patients, the Milwaukee protocol precludes the administration of anti-rabies antibodies.

Does the success of the Milwaukee protocol suggest that clinical rabies is finally a curable disease? Several issues need to be addressed at this juncture. Most importantly, this medical procedure carries an unsatisfactorily low success rate: it has saved only 6 out of the 35 patients on whom the protocol was attempted. Also, it has shown benefit only in rabies acquired from cats and bats. Since dog bite transmitted rabies is believed to harbor the most virulent form of the virus, curing canine origin rabies in humans would remain the gold standard for future trails.

It must be mentioned at least in passing that a spate of criticism against the use of this protocol has arisen from a section of the medical community who believe that rabies may not be the uniformly fatal disease that one attributes it to. The critics point out the possibility that the survivors may have been infected by a less virulent form of the virus or that they may have the capacity to mount extremely strong immune responses. Indeed, the case against the Milwaukee protocol is akin to the one that uprooted the practice of radical mastectomy for breast cancer instituted by William Halsted in oncology. When the practice of progressively more extensive surgery was being touted as the miracle surgical cure for breast tumors, it was subsequently realized that
surgical success and survival from breast cancer is not borne upon by the extent of the surgically removed tissue. Rather, long term outcome is decided by the stage of the disease at clinical presentation. In a similar vein, does survival from rabies depend only on the nature of the virus-host relationship irrespective of the treatment protocol used?

Whether the Milwaukee protocol actually offers significant clinical benefit is a question that only further trails will tell. But the efforts of Dr Willoughby, who epitomized rational medical research at its best through the Milwaukee protocol, have turned a page in medical history.

References


2. A detailed guide on the Milwaukee protocol for medical practitioners has been made available by the Medical College of Wisconsin on its website http://www.mcw.edu/FileLibrary/Groups/Pediatrics/InfectiousDiseases/Milwaukee_rabies_protocol_V3_1.pdf).