

## Sedation-Paralysis as Cornerstone on Rabies Management (Milwaukee Protocol)

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### ARTICLE INFO

#### Article history:

Received 12 August 2021

Revised 02 September 2021

Accepted 17 September 2021

#### Keywords:

Sedation-paralysis;

Rabies;

Milwaukee protocol

### ABSTRACT

Rabies is a viral infection involving the central nervous system that is almost always fatal without proper post exposure prophylaxis. Here, we present a 38 years-old male with dog-bite and late attention whom, managed in intensive care unit. After 21 days, the disease progressed to serious neurologic and hemodynamic damage including motor disorders and imbalance in blood pressure and cardiac rhythm. Clinical management of the patient consisted of antiviral agents (Amantadine and Ribavirin), neuroprotection, sedation-paralysis and supportive care. Patient was survived 43 days from the clinical disease onset. Although our patient died in spite of intensive care, advances in the use of sedation-paralysis and early prescription of antiviral agents raised hopes that it may eventually be possible to save rabies patients.

Rabies is a fatal disease in humans and survivors of the disease usually, have received rabies vaccine and serum immunoglobulin before the onset of illness [1-2]. Rabies can manifest itself in three forms: classic encephalitic, paralytic, and non-classic atypical rabies. All forms are progressive and usually lead to death [3-4]. Hyperexcitability, autonomic dysfunction, and hydrophobia are characteristics of encephalitic rabies, and quadriplegia with sphincter involvement are characteristics of paralytic rabies [5]. Paralytic rabies presents with flaccid muscle weakness, and can be confused with Guillain-Barré syndrome. The non-classic atypical rabies usually occurs following exposure to the bite of a bat, but has also been described after dog bites and presents mostly with neuropathic pain, focal brainstem signs, and myoclonus amongst other neurological symptoms [1, 3, 6].

Several tests are available to confirm the diagnosis of rabies: reverse transcriptase polymerase chain reaction

(RT-PCR), serology, direct fluorescent antibody test and viral culture [7].

This case report shedding a light to treatment of rabies as previously the dominant approach to management of the rabies was palliative and post exposure.

### Case Report

A 38-years-old married farmer male, with no preceding medical illnesses, was admitted to the intensive care unit (ICU) of an academic hospital in Northeast of Iran.

He was visited in an outpatient clinic complaining of fatigue, tingling and numbness of legs with intermittent muscle spasms. He experienced pain and numbness in lower limbs and a flushed sensation throughout his body from 9 days ago (10th day after dog bite). Progressing these symptoms; he felt unsteady and nausea, dysphasia and inability to drink. He was somewhat confused but answered questions appropriately and complied with

The authors declare no conflicts of interest.

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commands. His wife reported increased sweating and libido in him during last week.

He was examined by a general physician in outpatient clinic and rabies vaccine and immunoglobulin were prescribed. Appropriate samples of saliva, skin and hair follicle was obtained then the patient was referred to a secondary hospital due to suspicion to rabies. At that time, blurred vision and diplopia have been developed. He was afebrile, obtunded but able to follow commands.

In the local hospital, lab data showed mild leukocytosis ( $12.5 \times 10^3/m^3$ ) with 80% PMN and 16% lymph; Hb=15.9 mg/dL, PLT count was  $306 \times 10^3/m^3$ . BUN and Cr was 65 mg/dL and 1.1 mg/dL, respectively. Na and K were reported 143 meq/dL and 3.9 meq/dL, respectively.

Antiviral agents (Ribavirin and Amantadine) and IV antibiotic (Cephalothin) were prescribed to the patient, and then he was transferred to our academic hospital for intensive care managements.

At admission time in Intensive Care Unit (ICU), patient was lucid but markedly agitated, and unable to swallow due to involuntary inspiratory muscle spasms. On physical examination he was afebrile, and had a dry mouth, normal heart rate and blood pressure, and a Glasgow Coma Score (GCS) of 12 out of 15. He had bilateral pupil dilatation (5 mm) with weak direct and consensual light reflexes and partial bilateral sixth-nerve palsy. He had no focal neurological signs and no neck stiffness. His skin showed evidence of old bite injuries on cuff of right lower extremities.

When taking history, a wild dog bite has been reported 19 days prior to referring to the outpatient care. Ten days after the dog bite his symptoms have been started to present.

During the next 48 hours after admission in ICU, a temperature of 38.60C has been recorded. Also slurred speech, difficulty in eating (dysphagia), drinking and speaking, decrease in level of consciousness, increased lethargy, nystagmus and occasionally panic attacks, muscular twitching and stiffness, impaired muscular coordination and tremors in the extremities have been reported.

Patient's Brain Computer Tomography scan (CT scan), Magnetic Resonance Imaging (MRI) with and without contrast and Magnetic Resonance Angiography (MRA) studies reported normal.

Advanced hemodynamic monitoring was applied and patient transferred to a dark, isolated, comfort room in ICU. He was sedated by diazepam and morphine sulfate to manage patient's critical condition and he was paralyzed by pancuronium (0.05 mg/kg/h). He was intubated by appropriate cuffed orotracheal tube and was supported by synchronized intermittent positive pressure mechanical ventilation.

No lumbar puncture (LP) was performed, because the rabies diagnosis was established before by saliva and hair follicle examination in Pasture Institute of Iran (Tehran

and Amol city). Direct fluorescent antibody staining of hair follicles and nuchal skin biopsies was positive for viral antigen. Rabies-virus RNA was detectable by reverse transcriptase polymerase chain reaction (RT-PCR) assay of either sample.

After 21 days that was noted as a prolonged survival time, diverse and seriously hemodynamic changes have been developed. Contrary to drug-induced coma, ventilator support and disenfranchisement of vexing stimulation; severe tachy/ brady arrhythmia and unstable blood pressure have been presented. Perforce; we prescribed sympathomimetic or sympatholysis and vasopressor agents for controlling this new condition. Although, after one week the hemodynamic oscillation was under control but the general condition of patient from neurological point of view was overthrow.

Our patient died after 43 days of dog bite, in spite of intensive care, antiviral agents prescription and sedation/paralysis because of insufficient cardiovascular system due to autonomic and neurological failure.

## Discussion

Our case presented with an acute progressive encephalopathy in which a prominent symptom was not specific but there was a clear history of wild dog bite. There were no clinical signs of meningismus supporting a diagnosis of bacterial meningitis. Tetanus was considered unlikely as no muscle rigidity and trismus were seen in our patient. Acute disseminated encephalomyelitis, Encephalopathy, Guillain-Barré syndrome, Myasthenia Gravis and Botulism was ruled out by clinical manifestation, physical examination and history taking.

Clinical manifestation of our patient was spastic encephalopathy with neuropathic pain, muscle spasm and nonspecific symptoms but the majority of the cases present as encephalitic rabies, with hydrophobia and hyper-excitability. Early clinical features of rabies are nonspecific prodromal symptoms and local neurological symptoms, including paresthesia, pain, and pruritus at the site of virus entry [4].

Suitable specimens for rabies detection are saliva or a buccal swab, skin biopsy from the nape of the neck (containing hair follicles with nerve endings) and cerebrospinal fluid (CSF). Serology can be performed on serum and CSF, but is of little immediate diagnostic value in the acute stage of the disease as rabies antibodies are generally not formed before the second week of illness [5,7-8]. Molecular techniques, like RT-PCR, for rabies are becoming more widely available in developing countries [5, 7-8]. In our patient diagnosis of Rabies was established by saliva and hair follicle examination in Pasture Institute of Iran (Tehran and Amol city).

In 2004, Wisconsin Division of Public Health reported the first documented recovery from clinical rabies in a

patient who had not received either pre/post exposure prophylaxis for rabies. Rabies was almost invariably fatal disease for a long time [7]. A small number of survivors have been reported [1-2]. These patients, who developed rabies after being bitten by a bat were treated with a combination of supportive care, a drug-induced coma, and antiviral treatment with ribavirin and amantadine, known as the Milwaukee protocol. So, we must make a serious decision to use an aggressive approach to treat patients who present in late stage of clinical disease.

Even with intensive care, the majority of patients with rabies do not survive for more than 3 weeks [9]; No single therapeutic agent is likely to be effective. Treating with a single agent, such as ribavirin or IFN- $\alpha$ , has been unsuccessful, although a combination of specific therapies may be more effective. 5,10 Ribavirin has in vitro activity against rabies virus infection, although no efficacy was demonstrated in animal models. There is limited information about its penetration across the intact blood-brain barrier [5,10]. We considered a combination of specific rabies immunoglobulin, monoclonal antibodies, Amantadine and ribavirin accompanied by induced coma.

Our patient was referred to an academic hospital for intensive care. Neurological symptoms and medical complications of the rabies patient need to be anticipated and can partly be managed with the use of sedatives-Hypnotics, narcotic analgesics and neuromuscular blockers [7]. The dismal outcome of patients with rabies provides little optimism for heroic efforts, based on the review literature we applied sedation and paralysis approaching to deep comatose state and burst suppression.

There are reports that suggest ketamine for sedation. Ketamine is a noncompetitive antagonist of the N-methyl-d-aspartate receptor. It rapidly crosses the blood-brain barrier. Ketamine has been demonstrated to inhibit the in vitro replication of rabies virus by inhibiting rabies virus genome transcription [11-13].

Haloperidol with or without diazepam were found to improve palliative care but, the efficacy differs per patient and requires tailoring [1,4]. Ketamine stimulates saliva secretion and induced dissociative sedation and hallucination. So, we preferred to use a combination of Diazepam, Morphine sulfate and Pancuronium according to patient's condition for deep coma induction.

## Conclusion

This experimental regimen in our patient was not successful, and he died after 43 days. Milwaukee protocol could not save our patient but it could keep him alive for extra days. Rabies comes with agonizing symptoms and no therapeutic protocol for rabies in humans has been demonstrated to be effective. Its outcome is dependent on neurologic performance, therefore rabies vaccine and

immune globulin as post exposure prophylaxis treatment, induced coma, antiviral agents (Amantadine and ribavirin) and intensive care as a treatment strategy are the cornerstone of rabies management. There is a need for recommendations on how to provide intensive care for rabies patients in our settings.

## Acknowledgments

The findings in this report are based on data reported by Intensive care unit staff of Shahid Sayad Shirazi educational hospital, Gorgan city, Northeast of Iran.

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