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Case Report

Clinical rabies: is cure possible?

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ABSTRACT

Rabies is a fatal disease in humans and till date survivors of the disease after the clinical onset of the illness are rare. The approach to management of rabies is usually palliative. In rare cases of paralytic rabies a trial for cure has been tried. No single therapeutic agent is likely to be effective, but a combination of specific therapies could be considered, including rabies vaccine, rabies immunoglobulin, monoclonal antibodies, ribavirin, interferon alpha, ketamine etc. the only reported cases in literature were with rare success of the Milwaukee protocol. This is the case report of a 45 year old male who presented with clinical rabies and was started on the trial. Has the treatment had any benefit is to be debated and further options discussed.

Keywords: Rabies, Milwaukee protocol, Therapeutic coma

INTRODUCTION

Rabies is a zoonosis caused by the genus Lyssa virus of the family Rhabdoviridae. The bullet shaped rabies virion contains a single strand of RNA of negative polarity. Inoculation of rabies virus into a wound or on to a mucous membrane or with organ transplants may result in infection. Rare reports of inhalational spread in bat infested caves are found in literature. Though rabies is not known to cause infection from human to human other than through organ transplantations; it is advisable to take universal precautions when dealing with patients.

The interval between inoculation and the onset of symptoms is between 3 weeks to 3 months but may prolong upto years. In general the nearer the bite is to the head, the shorter the incubation period. The illness may have a short prodrome characterized by itching or paraesthesia of the healed bite wound (40%) and other non specific features. The disease may then progress to clinical illness. Two variable presentations include – Furious rabies (80%) and Paralytic or Dumb rabies (20%). Furious rabies presents with stage of encephalitis characterized by hydrophobia, aerophobia, and sometimes opisthotonus and convulsions resulting in coma and death. Other features like myocarditis, signs of dysautonomia like increased lacrimation or salivation and rarely increased libido, priapism and spontaneous orgasms may occur. Paralytic rabies is less common than furious rabies and results in prodromal symptoms followed by weakness and hypotonia. The ascending paralysis may involve bladder and bowel as well as respiratory involvement later. Hydrophobia and aerophobia is rare and seen in late stages.

Treatment of rabies till date has been effective only in the prophylactic approach where vaccines and Immunoglobulin give 100% protection. But the management of clinical rabies is still restricted to palliative approach. Attempts and trials have been made to find a protocol for curative treatment but with little success. Till date only seven individuals have survived rabies after its clinical onset. All of those cases had received some form of pre or post exposure prophylaxis

except one patient. No single treatment regimen has consistently proven effective for the management of human rabies.

The Milwaukee Protocol

A variety of approaches have been used in the treatment of human rabies, and a recent protocol was developed by the Medical College of Wisconsin - the Milwaukee Protocol - after the survival of a young patient from Wisconsin diagnosed with rabies. In the case of this survivor, induction of a therapeutic coma in addition to supportive care measures and antivirals were used with success. A number of agents were used to induce a therapeutic coma to decrease the metabolic demands of the CNS, theoretically reduce possible excitotoxicity of rabies, and diminish autonomic hyperactivity associated with progressing clinical rabies. But later on the attempts to duplicate the protocol have proven not successful ever since.

CASE REPORT

A 45 year old male patient who was a farmer leading a normal life and residing in a place near to forest area had an acute onset of fever and difficulty to drink water.. Breathing difficulty was noticed on and off in the form of fast breathing and tightening of neck muscles on exposure to water lasting for a few minutes. Preceding symptoms of body pain and pain and tingling sensation over a wound scar on the nose was noticed. He had difficulty to swallow liquids but was feeling thirsty. After 1 day he developed weakness of the left upper limb and shooting pain preceded by paraesthesia of the limb. No sensory or motor deficit was noticed in the other three limbs. His wife noticed minimal slurring of speech associated with the episode and towards the end of the day he had paraesthesia of the tongue also. He consulted a doctor and was referred.

He was having a history of an unidentified animal bite to the nose and the left upper limb 2 ½ months prior to the illness. Though medical consultation was done immediately no antirabies prophylaxis was taken and the wound was sutured. He was giving a history of emotional distress and irritability without any identifiable stressors and dyspepsia 1 week prior to the onset of illness. He was not having any other illness for which he was on medication in his past. He was a c/c pan chewer and an occasional alcoholic. There was no history of change in habits as to suspect alcohol withdrawal symptoms.

On examination he was moderately built and nourished. There was no pallor, jaundice, cyanosis, clubbing, lymphadenopathy or pedal edema. His pulse rate was 90/ min and regular. BP was 130/80 mm Hg and there was no orthostatic hypotension. His respiratory rate was normal but there were intermittent episodes of breathing difficulty in the form of fast breathing with inspiratory spasms. There was no dyspnea in between the episodes. Hydrophobia and Aerophobia were present. His neurological examination showed normal higher mental functions. There were decreased corneal and conjunctival reflexes bilaterally. Minimal sensory deficit for pain, touch and temperature was noticed on the left side of the face. There was demonstrable weakness of both sternocleidomastoid and trapezius muscles with only grade 4 power. All the other cranial nerves were normal. His motor system examination revealed hypotonia of neck muscles and both upper limbs with more affection on the left. Normal tone was noticed in all other muscle groups. Power was only grade 1 in all the muscles tested in the left upper limb. Grade 3 power was noticed in the right upper limb. Other muscles showed grade 5 power. Deep tendon reflexes were lost in the left upper limb and were sluggish in the right upper limb. Tendon reflexes in the lower limbs were normal. On eliciting the plantar it was found to be inconclusive with an exaggerated withdrawal response with tremors of the foot lasting for a few seconds on stroking the sole. No ankle or patellar clonus was elicited. Primitive reflexes were not present. Sensory system examination revealed decreased primary modalities of sensations on the left side of the face and both upper limbs. No extra pyramidal or cerebellar signs were elicited. There was no neck stiffness and skull and spine were normal. Examination of other system examination did not reveal any abnormality.

So with the available history and clinical findings a diagnosis of Paralytic Rabies was made. Patient was kept in isolation room in ICU shut off from light and other sensory stimuli. Though his vitals were stable he was found to be deteriorating fast with episodes of dyspnea occurring more frequently. Informed consent for the therapeutic trial was availed after explaining the risks and limitations

His investigations like Blood routine examination, LFT, RFT, Serum Electrolytes were all normal. Arterial blood gas analysis was normal. C T Scan of the brain was normal. A corneal imprint smear and nuchal skin biopsy was prepared and sample was sent to Pathologist for evaluating the possibility of rabies.

Though the investigation reports were pending a decision was made on clinical grounds for the trial to cure, The Milwaukee Protocol. With the help of the Anesthesiologist, therapeutic coma was induced in the patient and mechanical ventilation started within 6 hrs of admission. Though there were conflicting data on use of HRIG (immunoglobulin) we decided to give it to the patient and a total dose of 1500 IU were given as intramuscular injection. The medications used in the patient were

I. Inj. Ketamine 100 mg/hr IV infusion
II. Inj. Midazolam 50 mg/hr IV infusion
III. Inj. Thiopentone or Inj. Diazepam 5 mg IV sos
IV. Antivirals
    a) Ribavirin 1g / day

b) Amantadine 200 mg/day
c) Acyclovir 500mg IV Q8H

V. Phenobarbital

Antibiotic prophylaxis, IV Fluids, Antipyretics and other symptomatic supports were started. Prophylaxis for preventing venous thrombosis was initiated after 2 days. His vitals and metabolic parameters were monitored and maintained within normal range. Central venous pressure was monitored continuously and kept between 8 – 12 cm of H_2O. Daily ABG analysis was done and ventilator settings adjusted accordingly. The electrolyte imbalances were corrected with IV supplementation.

On the first day the patient was having high spikes of fever and was controlled with antipyretics and tepid sponging. Signs of dysautonomia were present. Hypersalivation and frequent ventricular and atrial ectopics were identified. Hypotension detected from 3rd day was treated with inotropic support with Dopamine. In the subsequent days the patient had more frequent ectopics. Hypersalivation got aggravated. BP monitoring showed occasional fall for which Noradrenalin drip was started. His urine output was adequate and fluids were replaced according to input output chart and CVP monitoring. The results of the corneal imprint smear and nuchal skin biopsy was found to be positive for rabies virus. However inconclusiveness of these investigations were kept in mind though a decision to continue with the protocol was made on clinical grounds. By the end of 4th day he had edema with more involvement of face and upper limb. Acyclovir was stopped after 5th day. His condition was maintained with close monitoring of vitals till the end of day 8. By 9th day the patient was showing signs of minimal improvement. Daily salivary output was being monitored and it showed a significant decrease from 9th day onwards. His cardiac monitor was showing a significant improvement in the regularity of the rhythm with only occasional VPCs when compared to earlier. By day 10 the monitor was showing continuous sinus rhythm. The cardiac supports were tapered and BP got stabilized without pressor support. The edema decreased in severity. A CSF sample was obtained and was sent to Department of Neurovirology, NIMHANS for evaluation and to decide on the further management. The patient's relatives were finding difficulty to meet the expense of the treatment and on request, Diazepam as an alternative to the more costly Midazolam was initiated in a dose of 30 mg/hr IV infusion. 11th day of treatment early morning the patient had a sudden cardiac arrest for which the cause was not identified. After resuscitation the monitor was showing frequent ectopics. The electrolytes, RBS and the ABG was checked and ensured to be normal. Patient had recurrent episodes of cardiac arrest and after the 5th episode resuscitative measures failed and he was declared clinically dead and the ventilator disconnected.

The CSF and serum result was obtained from NIMHANS later and was found to be positive. The antibody titre was found to be 1: 64 in serum and 1: 16 in CSF (Rapid Fluorescent Focus Inhibition Test).

DISCUSSION

Treatment of rabies has always been limited to the proven efficacious methods for prophylaxis both preexposure and postexposure. Though protocols for treating the patients with clinical rabies have been tried the efficacy of those was found to be alarmingly low. Only about 7 cases have been found in literature which escaped after the onset of the illness. Of them except one, all had received anti rabies vaccination or serum in complete or inadequate doses. The first ever reported case of successful treatment is that of a young girl who was treated in the Medical College of Wisconsin by the Milwaukee Protocol.

In our patient the decision regarding treatment was a difficult one as the outcome of curative trials was not encouraging. The limited success rate and the cost of therapy was informed to the relatives and after their decision to go with the trial for cure, a team consisting of Physicians and Anesthetist was called in for the treatment decisions. The initial treatment had to be planned strictly based on the clinical diagnosis as the delay in waiting for the investigative confirmation would cause the patient to deteriorate.

Classical signs of the illness like hydrophobia and aerophobia as usually seen in the early phases of furious rabies. Very rarely they can be seen in association with paralytic rabies towards the later stages. In our patient there were some rare findings like the association of hydrophobia and aerophobia even in the early days of the onset of the illness along with a paralytic picture. So the treatment protocol which was usually advocated in paralytic rabies were decided and initiated.

Supportive care was aimed to supplement and prevent nutritional deficiencies associated with severe illness. Also symptomatic management with antipyretics, mechanical ventilation and use of vasopressors were warranted to maintain normal homeostasis. Hypoalbuminemia was corrected with IV albumin. Seizure prophylaxis and DVT prophylaxis were started. IV Fluids were regulated monitoring the electrolytes, RFT and CVP.

Therapeutic Coma

The agents employed to induce and maintain therapeutic coma in our patient included Thiopentone, ketamine, benzodiazepines, and barbiturates. The rationale behind instituting a therapeutic coma relates to decreasing the metabolic demands of cerebral tissue, reducing autonomic hyperactivity and possible seizure activity that may occur in later stages of the disease, and inhibiting the possible excitotoxicity that may occur in rabies.

Ketamine, a dissociative anesthetic derivative of phencyclidine, was used at an infusion rate of 2 mg/kg/hour. Ketamine has proven antiviral activity in vitro. In vivo antiviral effects of ketamine are yet to be determined, although its use in the management of rabies may be beneficial from a sedation and antiviral standpoint.

Benzodiazepines have been used in a number of cases and so in this to aid in the maintenance of a therapeutic coma. The most common agents used include midazolam, lorazepam, diazepam, and alprazolam. Our case was maintained on Midazolam 1mg/Kg/hr infusion which had to be changed later to Diazepam 0.3mg/Kg/hr. Prolonged high-dose continuous infusions of preservative-containing midazolam may result in metabolic acidosis for which daily ABG monitoring was done.

If sufficient sedation is not achieved with ketamine in combination with a benzodiazepine, a barbiturate may be added as adjunct therapy. In our patient, Phenobarbital was added to the medical therapy to maintain burst suppression. Thiopental was kept as an alternative.

The duration of maintaining a therapeutic coma may vary from patient to patient. As recommend by the Milwaukee protocol, discontinuation of sedation and analgesia should occur when patients have mounted an adequate immune response by evidence of anti-rabies titers in the CSF exceeding 1:1024 by indirect immunofluorescence assay or 1:40 by rapid fluorescent focus inhibition test. Conversely, sedation may be discontinued if the patient has progressed to denervation of cardiac tissue, indicated by a lack of heart rate or blood pressure variability over a 24-hour period. At this point, the rabies virus has caused significant neuronal dysfunction and continuation of care may be considered futile.

Antiviral Therapy

A number of antiviral agents have been employed in the treatment of human rabies. In combination with a therapeutic coma, antivirals should aid in viral clearance and allow the patient to recover. These agents include ribavirin, amantadine, interferon Alfa, and acyclovir. In our patient antiviral therapy was started with a combination of Ribavirin, Amantadine and Acyclovir.

Based on the beneficial outcomes of the Milwaukee Protocol in the Wisconsin and Brazilian patients and the lack of successful alternatives, the implementation of the Milwaukee Protocol may be appropriate in certain cases. Rabies victims in whom the protocol may be effective include those who are healthy, immunecompetent and of young age, as was the case for both the Wisconsin and Brazilian survivors. Due to the high rate of mortality associated with rabies regardless of treatment, patients and families must be aware of the likelihood of negative neurologic outcomes and treatment failure that may result. Viral clearance from the brain of lethally infected rats has been achieved by treatment with a particular monoclonal antibody. No such treatment is available for man.

Induction of therapeutic coma was initiated within 6 hours of admission and the patient was showing signs of dysautonomia in the initial few days. The treatment was decided based on the case report from Wisconsin in the literature with minimal modification as per institutional and individual needs. Initial few days witnessed the well known complications of the disease setting in. But towards the later days there were signs of improvement initiating signs of hope that the protocol might prove effective in this patient. His hypersalivation had decreased and the cardiac monitor was showing sinus rhythm. The metabolic parameters were well within normal range. The dose of supportive medications was tapered depending on the response. But on the 11th day of treatment the patient went into recurrent cardiac arrest and was declared clinically dead. The cause of sudden cardiac arrest might be postulated to be the effect of a dysautonomic event as all the other causes like electrolyte imbalance and metabolic factors was ruled out. The possibility of myocarditis could be another cause for the lethal complication as the rabies virus is well known to produce viral myocarditis. In an effort to protect against this he was already on antivirals like Ribavirin which has got a protective effect in myocarditis. In spite of the best effort and trial we lost the patient.

Though the trial was not successful there were rays of hope when we treated the patient. The disease activity during treatment was showing some sort of remission possibly which may be interpreted from the decrease in signs which should have got worse in the natural course of the illness the patient had. Though there were no reports of human to human transmission; it is advisable to take universal precautions by health personal when treating patient with rabies. In our institute the faculty involved in undertaking the trial was vaccinated with antirabies vaccine. Autopsy was not done in our patient as the relatives were not willing for the same.

CONCLUSION

The decision to adopt the therapeutic trial was taken though in the background of limited hope of success with the informed consent of the relatives. Every success comes from repeated trials and the decision to take the chance for the trial. So in patients who have got the indication for giving a trial should be opted for the same with informed consent. In our patient we faced many difficulties right from the point of making a decision in treatment protocol. The effectiveness of the treatment we instituted though failed may be debated the evidence of not such high titre of antibody in CSF in our patient as seen in cases of paralytic rabies proved to be of some hope for future. The experience gained from the trial may help future patients. As research advances new agents may become available in the future treatment of human rabies. The experience in trying to cure the disease may

provide some information for the better understanding of the disease process and better management of future patients.

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