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Case Report Open Access

The Rare Case of a Human Rabies Survivor & the Comparative Study of All Documented Human Rabies Survivors Till 2021

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Abstract

Derived from a Sanskrit synonym "Rabhas", meaning "violence", Rabies, is a violent outrageous infection of the brain1 recognised in Vedic Indian scriptures dating to a period as back as 1500 B.C. Very deadly, rabies has been described as 'the dog accompanying The God Of Death'.

Rabies is a fatal zoonotic viral disease transmitted from mammals to humans, that's characterised by an acute excitogenic encephalitis and generalised paresis.

With only 24 documented cases of survival worldwide, till date, post development of symptoms, we are hereby reporting another classical case of rabies, which underwent gradual recovery, with minimal neurological sequalae.

Keywords: Human rabies; List of survivors; Indian study; Rare case report; Milwaukee protocol; Largest comparative study

Introduction

Derived from a Sanskrit synonym "Rabhas", meaning "violence", Rabies, is a violent outrageous infection of the brain1 recognised in Vedic Indian scriptures dating to a period as back as 1500 B.C. Very deadly, rabies has been described as 'the dog accompanying The God of Death' [1].

Rabies is a fatal zoonotic viral disease transmitted from mammals to humans, that's characterised by an acute excitogenic encephalitis and generalised paresis [2].

With about 99% of cases being dog bite mediated, almost any mammal (domesticated or wild) is capable of incubating and transmitting the virus. The Rhabdovirus (RABV), of Family Lyssavirus is responsible for around 59,000 deaths worldwide annually, accounting to more than 60% of the deaths within India, owing to its lesser surveillance because of not being categorized a notifiable disease [3].

With only 24 documented cases of survival worldwide, till date, post development of symptoms, we are hereby reporting another classical case of rabies, which underwent gradual recovery, with minimal neurological sequalae.

Case Report

Our case, hereby, is a young female, aged 33 years, who was brought to the Emergency Room, by her husband and relatives, at around midnight of 28th September 2017 [4].

Giving a prompt history of a wild animal (Indian Civet, Viverricula indica) bite on her right leg 18 days back, the patient was now brought to our hospital, with complaints of altered sensorium for past 5-6 hours, with gradual deterioration to generalized immobility and non-responsiveness for past 2-3 hours [5]. The patient was brought from NICD (National Institute of Communicable diseases), New Delhi, where the clinical diagnosis of "Acute Rabies Viral Encephalitis" was made. The attendants were counselled there for an isolation room for the patient, with a fatal prognosis succeeding it [6]. Thus, well-aware of the outcome, the patient was brought by her husband, for the terminal hospice care and palliation.

Admitted with us under Intensive Care Unit, the patient was examined, elaborately. The patient was in an unconscious state, responding by wincing (but with no withdrawal) to deep painful stimulus [7]. Her blood pressure was 130/90 mmHg, heart rate was 126 bpm, pulse rate 124 bpm, with no irregularities. Her respiratory rate was 24/min and, she was afebrile with an axillary temperature of 98.4 degree Fahrenheit [8]. Her saturation, on a pulse oximeter, displayed 94% at room air, and there were no signs of any respiratory distress. Upon further examination, both her plantar reflexes (Babinski's) were flexors, both her pupils were normal sized, sluggishly reactive [9]. There was no neck rigidity, but, all other deep and superficial reflexes were diminished. Tone of her muscles were intact, and power was not elicitable. There was no history or any finding suggestive or urinary or bowel incontinence.

Her chest was clear, with normal vesicular conducted sounds, and the heart sounds were normal. Her right leg's lateral aspect had a wound, which was dressed antiseptically [10]. The wound, upon exposure, had multiple lacerations, imprinting the bite marks of the animal (mentioned above), each 2-3 cm deep, with localised surrounding rubor. Patient was catheterized for urine, keeping her sensorium in view. There was no history of any abnormal body movements, any frothing from mouth, tongue bite [11].

Upon retrograde history, her husband, who witnessed the incident had explained of an unprovoked bite by the animal, in the wake of light (around 5am IST) [12], which ferociously kept held on to the patient's leg, until it was killed. Immediately, the patient was taken to a local physician, the wound was washed and antiseptically dressed [13]. The

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wound was bleeding actively. The patient was started on Anti-Rabies Vaccine (Rabipur/Verorab), within 4 hours of bite, along with a stat dose of Tetanus toxoid, and was immunised regularly, as per the WHO guidelines, on Days 0-3-7-14 thereafter [14]. No local immunoglobulins were given. The patient was brought home immediately, prescribed on symptomatic medications.

But, 3 Days post-Bite, the local (bite-site) residual pain , started aggravating , and the over next 4-5 days, the patient used to vividly explain , the radiation of pain, beginning from the leg extending to the chest, and then progressed to the head, manifesting as a severe headache by Day-9 post-bite and patient was admitted for the same in a local hospital [15]. The patient started developing anxiousness, restlessness, and could not sleep, until was sedated, 10th day onwards (post-bite). On Day 15 post-bite, patient developed fever (high grade), along with multiple episodes of vomiting, incompletely responsive to medications [16]. It was when the patient started refusing water, with inability to swallow (Hydrophobia: Pathognomonic of Rabies), that the patient was referred to NICD, New Delhi, suspecting Rabies Encephalitis [17].

Upon leading with questions further, the husband also gave a vague history of the patient exhibiting intolerance to light (Photophobia) while driving from hospital to hospital in his car, resistance to air on switching on the ceiling fan or opened windows while moving the car (Aerophobia) and inability to produce proper phonation (aphonia) preceding the current comatose state of patient's presentation, all presenting since 11th day post-bite [18]. The restlessness, irritability progressed immediately, with the patient not slept at all for past 3-4 days before her presentation to our hospital.

Post her admission in our hospital, the patient was duly investigated. All her blood and serum investigations were non-significant except Renal function test, CSF examination and Magnetic resonance imaging of Brain [19]. Her renal function test was deranged with Urea = 88.0, Creatinine = 2.2 with reduced and dark coloured urine output (about 300-400ml per 24 hours), but with no alteration in Kidney echotexture / morphology (as examined on ultrasonography) [20]. The CSF fluid was clear, colourless with RBS = 74mg/dl, Proteins = 130mg/dl, TLC = 120 cells with 90% lymphocyte predominance in cellularity. The MRI Brain showed features of encephalitis, probably of viral aetiology [21].

The patient was then palliatively managed conservatively with antimicrobial agents (Acyclovir, Ceftriaxone) with an emphasis on hydration [22]. Keeping the most probable diagnosis as-'Acute Rabies Viral Encephalitis', palliative approach to manage the patient's vitals and preventing her condition from further deterioration was primarily aimed, since most viral illnesses are self-limiting within 1-2 weeks [23].

Falling blood pressure was managed by adequate hydration, with monitoring of urine output, and regular blood sampling for renal function follow-up [24]. Any bradycardia was improved by Atropine on SOS basis. Regular suctioning using laryngoscope, nebulization and chest physiotherapy was done to maintain any respiratory inadequacy, with a mechanical ventilator kept on stand-by [25]. Limb physiotherapy, TPN (Total Parenteral Nutrition) was added for a generalised appreciable response. Maintained mostly in propped -up position, regular visits by her husband, brother , relatives were encouraged to boost her morale, as patient's positive will was also primarily paid heed to once her sensorium started improving [26].

Miraculously , by Day 7 post-admission (Day 23 post-bite) , the patient responded positively with eye opening on touch ,followed by gradual improvement to spontaneous eye opening, with interspersed periods of varying conscious levels (lucid intervals) ,over the next 6 days [27]. On Day 13, the patient started showing signs of further improvement by accepting oral sips, and on day 20 (post-admission), the patient was shifted to ward. She was now able to interpret verbal commands and respond by speech, but in bi-syllables. Nasogastric tube feeds were initiated, along with TPN (Total Parenteral Nutrition) [28]. The patient was typically aimed at being managed, by stabilizing through the periods of vital impairments and agitation, using sedatives and other counter drugs [29].

The patient underwent physiotherapy and speech therapy, until

Case no.	year	Age/sex	Place	Manner of infection	Immunization status	Type of rabies	Develop after	Confirmed by	Managed by	Recovery in	Sequalae
1.	1970	6yrs/M	USA	Bite on left thumb, by a Bat	Completed 14 Day course of Duck embryo rabies vaccine	Paralytic	20 days of bite	RABV isolated from the bat	Intensive care, Aggressively, Intubated	6 months	NONE[5]
2.	1972	45yrs/F	Argentina	Severe Dog bite	Delayed 14 daily doses of suckling mouse brain vaccine & 2 booster doses	Paralytic	21 days of bite	Rabies neutralizing antibodies in serum, CSF	Conservative management	13 months	MILD[6]
3.	1977	32yrs/M	USA	Laboratory exposure	Duck embryo vaccine pre-immunized	Paralytic	2 weeks	Info not provided	Intensive care, supportive	5 months	SEVERE[7]
4.	1994	9yrs /M	MEXICO	Multiple dog bites on face	4 doses Vero vaccine & 2 doses human diploid cell culture vaccine	Paralytic	19 days of bite	Peak serum & CSF rabies neutralizing antibody titre	Intensive care, on ventilator	3 weeks, (Died after 3 years)	SEVERE[8]
5.	2002	6yrs/F	INDIA	Dog multiple bites on hand, face	3 doses Purified chick embryo vaccine	Furious	20 days of bite	Rabies neutralizing antibodies in serum, CSF	Conservative With steroids	6 months	SEVERE[9]
6.	2004	15yrs/F	USA	Bat bite on left index finger	No vaccination	Paralytic	1 month	Rabies neutralizing antibodies in serum, CSF	Milwaukee protocol	5 months	MILD[10]
7.	2007	5 yrs /M	Equitorial Guinea	Dog bite on neck	No vaccination	Furious	5 weeks	PCR positive saliva, FAT positive skin biopsy	Milwaukee protocol	20 days	DEATH [11] (due to malnutrition)

8.	2008	15yrs/M	BRAZIL	Vampire bat bite	4-day delayed , 4 doses of vaccine taken	Paralytic	6 days	PCR positive skin biopsy	Milwaukee protocol	1 month	MILD[12]
9.	2008	17yrs/M	TURKEY	Forearm and shoulder bite by dog	1 dose of Verorab ,given 4 days later	Furious	21 days	RT-PCR in CSF,Saliva, FAT corneal smear-positive	Supportive, in isolation.	66 days	NONE[13]
10.	2009	17yrs/F	USA	Cave Bats exposure	No vaccination	Abortive	2months	Rabies neutralizing antibodies in serum, CSF	Conservative management (on outpatient basis)	15 days	NONE[14]
11.	2011	8yrs/F	USA	Multiple Cat scratch history	No vaccination	Paralytic	2months	Rabies neutralizing antibodies in serum, CSF	Intensive care, with Intubation	2 months	NONE[15]
12.	2011	13 yrs/F	INDIA	Dog bite, (Grade III) on leg.	No vaccination	Furious	2 years	Rabies neutralizing antibodies in serum	Supportive , In-patient care	Not specified	NONE[16]
13.	2011	6yrs/M	INDIA	Grade III dog bite, on neck,back	3 doses chick embryo vaccine given	*Atypical	22 days	Rabies neutralizing antibodies in serum, CSF	Supportive treatment	1 month	SEVERE[17]
14.	2011	17yrs/M	INDIA	Stray dog bite on left calf	4 late doses of purified chick embryo vaccine	Furious	22 days	Rabies neutralizing antibodies in serum, CSF	Intensive care & supportive	3 months	SEVERE[18]
15.	2012	4yrs/M	SOUTH AFRICA	Dog bite on left ankle (grade III)	late 3 doses PEP given	Furious	23 days	Rabies neutralizing antibodies in serum, CSF	Intensive supportive care	3 months	SEVERE[19] (Bedridden)
16.	2013	25yrs/M	CHILE	Multiple dog bites on leg	1 dose of PEP vaccine given	Paralytic/ non-specific	3 weeks (21 days)	Rabies neutralizing antibodies in serum, CSF	Milwaukee protocol with ventilation	4 months	MILD[20]
17.	2014	16yrs/M	INDIA	Stray dog bite	4 doses of PEP given	Paralytic	1month	RT-PCR from nuchal skin-Positive	Intensive care with ventilator	3 months	SEVERE[21] (pituitary cachexia)
18.	2014	13Yrs/M	INDIA	Dog bite	3 doses of Rabipur given	*Atypical	1 month	RT-PCR from nuchal skin,corneal smear- Positive	Intensive Aggressive support care	6 Months	SEVERE[22]
19.	2015	13yrs/F	INDIA	Unknown / unaware	No vaccination	Furious	20 days	RT-PCR,FAT for Rabies viral RNA,from CSF,nuchal skin-Positive	Intensive care, with Milwaukee protocol	1 month	NONE[32]
20.	2016	36yrs/M	GHANA	Dog bite Right leg	No vaccination	Furious	10 days	FAT on dog brain tissue-Positive	Intensive care with sedation	23 days	NONE[23]
21.	2017	33yrs/ F(The Current Article)	INDIA	Wild Badger, on the leg	4 doses of Pep taken	Furious	18 days	CLINICALLY	Intensive supportive care	1 month	MILD
22.	2017	14yrs/M	BRAZIL	severalBat biteepisodes	No vaccination	*Atypical	Non-specific (multiple episodes	Other victim's brain biopsy bitten by same bat	Milwaukee protocol	2months	MILD[28]
23.	2018	8yrs/M	INDIA	Dog bite on right hand	4 doses of Pep taken	*Atypical	20 days	Rabies neutralizing antibodies in serum, CSF, viral antigen	Intensive care with ventilator	3 months	SEVERE[29]
24.	2018	11yrs/M	INDIA	Dog bite on right hand (grade III)	5 doses of Pep taken	Paralytic	1 month	Rabies neutralizing antibodies in serum, CSF	Intensive care with ventilator	1.5 months	SEVERE[30]
25.	2019	4yrs/M	INDIA	Dog bite (grade III)	3 doses of Pep taken	Paralytic	2 weeks	Rabies neutralizing antibodies in CSF	Supportive treatment	1 month	SEVERE[31]

*_Atypical Rabies_, also known as '**Bat Rabies'**, have nonclassical signs-neuropathic pain, radicular pain, sensory motor deficits, and, in the prodromal phase, choreiform movements of the bitten limb. Brainstem signs and myoclonus occurs commonly with hemiparesis or hemisensory loss, ataxia, and convulsive and non-convulsive seizures; hallucinations are frequent [23].

Table 1: The List Of Brief Detailed Comparison Between All Documented Human Rabies Survivors Till 2021.

Day 33 (post admission) / Day 51 (post bite), when the patient showed the ability of independent voluntary movements, and was discharged with prominent dysarthria, quadriparesis of improving prognosis.12 months post-discharge, the patient was followed up on out-patient basis, persistent with a mild neurological sequelae of wide stepped gait and myalgia, but was independent enough to perform her household chores [30].

Hence, we confirm that the patient had outlived the acute phase of neurological system inflammation, with a mild physical residua [31].

Discussion

Most of the present day knowledge about rabies has evolved from in vitro studies using fixed (attenuated) laboratory strains, and thus cannot be accurately matched with highly non-specific features, in clinical settings [24].

How to diagnose rabies?

For a laboratory disease confirmation, WHO recommends brain tissue biopsy demonstrating virus antigen as 100% sensitive gold standard technique, but this technique is preferred in post mortem diagnosis. The antemortem diagnostic tests, are limited, and highly influenced by intermittent virus shedding, timing of sample collection, type of sample, and the type of rabies, reflecting the peculiar pathogenesis of the virus lacking a viraemic phase and evading exposure to the systemic immune responses [24], with the standard being the Fluorescent antibody test demonstrating the presence of viral antigen.

Is rabies treatable?

Though no aggressive management was required in this case, the non-specific spectrum of the classic rabies survival cases, had no patterned management technique, other than conservatively treating the patient until the proposed theory of hyperactive immune response (natural or artificial) with high antibody levels in CSF and serum, successfully led to viral clearance [24]. Table 1 provides a brief detailed list of rare documented rabies survivors worldwide, till date.

Conclusions

With the references taken from the study of 25 (including current case) survivors, in an otherwise 100% fatal rabies encephalitis in humans, the maximum number of cases have been reported from the Indian continent, which directly corresponds to the endemicity in the region. Most of the survivors observed to be of the younger age group, and also the survivors noted to be presenting with high titres of anti-rabies virus antibody, it showcases the potential of a healthy immune competent body, with a pressing importance of passive immunization, to counteract the disease. With 16 out of 25 survivors presenting in the non-furious type, a trend of survival has thus been seen in the non-aggressive form of rabies, thus also stating the role of virulence and strain of the virus, in prognosis. Clinical manifestation of the disease was faster with the bite closer to head and neck, though no significant variation in the recovery process. As in diagnosing, confirmatory ante-mortem tests from the laboratory need to be readily upgraded with recent most techniques and availability for prompt intervention and treatment, with RT-PCR climbing up the charts in reliability.

The 2009 case of Texas, USA, is the first case reported of Abortive type, where recovery from rabies without any conservative or intensive care was noted 19. 6 out of 25 survivors have been tried management using Milwaukee protocol, and though not much of a beneficial track record for the same has been reported earlier, it seems to have a marginal incidental benefit in survival of the patient, and proposed to be promoted in its usage as an additional support therapy to conservative management.

With most cases , recovering within the span of 2-3 months of conservative intensive management, 3-4 cases have extended for up to 6 months and only one case took 13 months of hospital stay, before discharge, suggesting the time span of aggressive approach required to wade through to survive, for a symptomatic case. As most of the cases, have had remnants of neurological disability, 7 out of 22 cases have ended with Complete neurological recovery with no or mild neurological sequalae. Hence, it is not only important to clear the virus from CNS but also to ameliorate the neuronal injury caused by the viral infection. Therefore, a combination of antiviral therapy, immunotherapy and neuro-protective therapy, should be an important area of research in animal models, to contribute in establishing an effective treatment and therapy of human rabies.

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