SPECIAL ARTICLE

Failure of Post-Exposure Treatment in Rabies Prophylaxis: Probable Cause

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Abstract

Introduction – Rabies is one of the ancient zoonotic diseases which is still a major health problem in India. Despite of availability of high potent modern tissue culture vaccine and most effective immunoglobulins, the disease still responsible for at least more than 12,700 of valuable human lives. As rabies do not allow the second chance to treat, the treatment protocol has to be very methodical, should be accurate and WHO guidelines and national guidelines to be followed strictly. In spite of following usual treatment in anti-rabies clinic, some cases of failure during the course of treatment have been observed. **Objective** – The main objective of this article is to pointing out the possible causes of failures, finding out the root cause and possible solution to this important aspect of management has been highlighted with determining causes and probable scientific based solutions. **Methodology** – Few cases reports from June 2009 to January 2019 with exclusion of Category I bites has been taken for studies. The place of study was conducted in New Delhi and Kolkata. **Results** – Mostly patients were children i.e. 60% belongs to age group between 15 years and 40% belongs to age group of 16 years and above. Incubation period was noted from 10 days to 7 months. Incubation period of one patient was recorded after 20 years as the virus was in dormant stage. **Conclusion** – The treatment protocol has to be very methodical following WHO and National guidelines along with APCRI recommendations for preventing treatment relating failures which is a most important aspect from treatment point of view.

Introduction:

M.V.I.D. Hospital, Delhi is the only specialized hospital for Rabies in whole NCR providing the management and isolation facilities of Rabies patients. The patients are referred to this hospital from all hospitals of Delhi and from neighboring states like U.P., Haryana, Uttarakhand etc. The overall situation of human Rabies has not changed over the past 10 years. An average 80 to 100 cases of fatal human rabies reported every year and admitted at MVID Hospital Delhi. In these cases, the victims generally did not receive prophylaxis. Approx. 30% cases had a history of partial vaccination or complete vaccination without RIG; and about 2% with RIG. Some cases also observed in Kolkata, West Bengal reported from 2009 to 2019 (January).

Objective:

To identify the reasons for death after Post-Exposure treatment. To ascertain the details of exposure site, severity of wound, risk of exposure and Post Exposure Prophylaxis.

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Materials and methods:

There was a long term study from 2009 to 2019 regarding the post exposure treatment failures. Eliciting the cause of failures despite of administering vaccine, pointing upon the possible causes and its implementation of the recommendation to prevent the cases of failures and to establish a proper guidelines particularly in case of severe category III bite. All category II and III cases are included in this series and category I cases are not included in the study. The results are distributed in tables and finally a thorough discussion has been done and conclusions were made followed by proposed recommendations.

Case 1:

History: A 5 years old male child from Okhala, Delhi admitted at I. D. Hospital on 10th Jan 2009 (after 20 days of exposure) with C/o Hydrophobia and expired on 11th Jan 2009. Patient was bitten by street dog on 21st Dec. 2008 at right hand with bleeding and reported to SJH. It was a category III Exposure. Wound toilet was not properly done.

Treatment given after bite: At SJH Rabies immunoglobulin was given after test dose and patient was advised for ARV treatment. Patient received 4 doses of ARV on D0, D3, D7, D14 & 5th dose (D28) was due. Dog was untraceable. IM dose was administered.

Probable Cause: Inadequate wound toilet. RIG not infiltrated in all wounds. 50% RIG misused on IM administration.

Case 2:

Subhajit Mondal, a boy of 4 years from Rajarhat area, Kolkata was bitten on face and left chest wall on 25th June 2009 by a suspected rabid dog which was untraced. He was reported to Pasteur Institute on 26th June, 2009 for **treatment** and advised to take rabid immunoglobulin and intradermal rabies vaccination on 26.6.09, 29.6.09 and 3.7.09. His body weight was 13 kg and received 520 IU ERIG locally. He ultimately developed high fever from 3.7.09, preceded by hydrophobia from 4.7.09 for which attended ID Hospital on 5.7.09 and expired on 6.7.09 in the morning.

Probable cause: high viral load, no wound toilet, immune status not ascertained.

Case 3:

An 8 years old female from Jatipur, Delhi was admitted at ID Hospital on 8.6.10. After 15 days of exposure with complaining of hydrophobia for 1 day. She was bitten by a stray dog on 23rd May, 2010 at left side of face and reported to RML Hospital on 24th May, 2010. The dog had bitten 8-9 persons but fate is not known.

Treatment given after bite at RML Hospital, rabies immunoglobulin given and advised for ARV. Patient received 4 doses of ARB on Day, 0, 3 ,7 and 14 and 5th dose was due.

Probable cause: Suspected rabid dog bite, immune status not known, received RIG and ARV 4 doses IDRV or IM. Wound toilet was delayed and inadequate. Faulty technique in administering RIG and vaccine may be responsible in management. Proper history not received. Other causes should come for consideration.

Case 4:

History: 3 years old female from Pushpa Vihar, Delhi admitted at I.D. Hospital on 19th Nov 2011 (after 14 days of exposure) with C/o Hydrophobia, irritability x 3 day and expired on next day. She was bitten by street dog on 5th Nov 2011 in upper lip, face and scalp. It was Category III bite and reported to Pt. Madan Mohan Malaviya Hospital.

Treatment: At PMMMH one dose IM –ARV was given & referred to SJH for ARS. At SJH as per body weight i.e. 11 kg ARS: 0.8 ml was given deep in gluteal region and rest 0.5 ml to be infiltrated around the wound and advice was given for ARV. Patient received 4 doses of ARV on D0, D3, D7, D14 & 5th dose (D28) due.

Dog was killed.

Probable Cause: Suspected Rabid dog bite, immune status not known, received RIG & ARV 4 doses, wound toilet was delayed and inadequate. Faulty technique in administrating in RIG and vaccine. Other causes fate not ascertained.

Case 5:

History: 52 years male admitted at I.D. Hospital, Delhi on 28th Dec 2011 (after 7 months of exposure) with C/o Hydrophobia, Aerophobia x 1 days. He was bitten by street dog on 19th May 2011 at dorsum of left hand and reported to Rao Tula Ram Hospital.

Treatment: At RTRH Inj. TT and ARV (D0) were given and referred to higher Centre for ARS. Patient reported to SJH on 20th May 2011. Rabies immunoglobulin was given with advice for loose suturing after 24 hours.

Rest dose of ARV taken from RTR Hospital (**D3**: 22.05.2011. **D7**:26.05.2011. **D28**:16.06.2011.)

Dog was untraced.

Probable Causes: Bite on 19th May, 2011 by stray dog on dorsum of left hand with a category III bite. Received rabies Immunoglobulin and ARV total 4 doses. The last dose was on 16.6.2011. All were IDRV doses. 50% RIG was administered in gluteal region. Patient was also treated with loose stitching in bite area after 24 hours. Again pointing towards variable and long incubation period of initial management that was poor. The stitched area may not properly infiltrated with RIG. Multiple prick during infiltration indicating opening of many ports for viral entry. A small transdermal puncture wound may have been missed and not irrigated, disinfected and injected with RIG.

Case 6:

History: 4 years old male from Moti bagh, Delhi referred from SJH & admitted at I.D. Hospital on 15th Aug 2012 (after 20 days of exposure) with C/o Hydrophobia x 3 day and expired on 18th Aug 2012. He was bitten by street dog on 27th July 2012 on right side of face. Category III bite and reported to SJH.

Dog was killed.

Treatment given after bite: At SJH Rabies immunoglobulin was given after test dose on same day and advice for ARV. Patient received 4 doses of ARV on D0, D3, D7, D14 & 5th dose (D28) due. Wound was sutured and dressed after RIG. Antibiotic and pain killer advised.

Probable cause: Treatment received with 4 doses of ARV and 5th dose was due (D28). Suturing of wound with inadequate wound toilet and faulty technique in administering RIG may be the cause.

Case 7:

A patient Bignaraj Paul, 26 years male admitted on 27.8.09 in Jehangir Hospital, Pune. Hospital registration no. was 357733 with history of irrelevant behaviour but mentally alert with hydrophobia for 1-2 days. He had a history of dog bite about 20 years back. He had history of long standing cough since 6.8.09 and reached Pune from Orissa on 7.8.09 following loose motion since 20.8.09, which ultimately stopped and developed itching and backache with muscle weakness particularly with the lower limbs and finally expired on 29.8.09 at 1 pm. His brain samples were sent to NIMHANS, Bangalore which confirmed presence of negribodies in the brain. For the past dog bite since he received ARV only 3 doses in different days.

Probable Cause: Virus may be in the dormant stage for long time and the incubation period is variable. Condition of biting dog was not known. Standard protocol was not maintained. Cause of death due to rabies.

Case 8:

History: A 05 years male child referred from PGIMS, Rohtak and admitted at I.D. Hospital, Delhi on 12 July 2013 (after 20 days) with C/o Hydrophobia, Aerophobia x 3 days and expired on 13 July 2013. He was bitten by street dog on 22 June 2013 on scalp and reported to PGIMS Rohtak within 2 hours of bite.

Dog was Untraced.

Treatment given after dog bite: weight: 12.86 kg. ERIG 250 IU IM stat & 250 IU were infiltrated in and around the wound at PGIMS Rohtak. Referred to Surgery for Stitch & wound management.

Antibiotics and pain killer Inj. ARV taken from General Hospital Jind on D0(22/6), D3(25/6), D7(29/6), D14(5/7) & D28 due on 20.06.13.

Patient received 4 dose of ARV on D0, D3, D7, D14.

Probable Cause: Inadequate wound toilet, stitching of the wound after RIG administration may be faulty technique, bite in the dangerous zone (face). Viral load may be was high. Height also important for transmission of virus which reached the brain earlier.

Case 9:

History: A 62 years male from Madhya Pradesh, referred from SJH and admitted at I.D.Hospital, Delhi on 31st Dec 2013 (After 35 days of bite) with C/o Hydrophobia & Aerophobia x 2 days and LAMA on same day. He was bitten by Hyena / wild animal on 26th Nov 2013 at both forearm and both legs. Bite mark was present. One another person was also bitten by the same animal. At present that person had no abnormality detected.

Treatment given after bite: Dressing of the wound was done after cleaning on same day. Inj. ARS & 5 dose of ARV were given as per schedule. Last injection was given on 24.12.2018. Documents were not available at the time of admission.

Probable causes: Wound toilet was inadequate, but another person was not affected. Due to increased viral load in the first subject / immune status also may be less with faulty technique of ARS infiltration and patient bitten by a highly rabid animal Hyena.

Case 10:

History: A 22 years male referred from SJH and admitted at I.D.Hospital Delhi on 02 Feb 2017 (after 16 days of bite) with C/o Hydrophobia x 3 days and expired on same day. He was bitten by a street dog on 18 Jan 2017 on face (multiple wounds) and reported to Govt. Medical College at Gwalior.

Dog was killed.

Treatment given after bite: weight: 62 kg. Inj T.T. RIG 8.3 ml infiltrated in & around the wound. ARV taken on D0(18/1), D3(21/1), D7(25/1), D14(1/2). D28 was due on 5.02.17. Wound was sutured and dressed after RIG. Antibiotic and pain killer advised.

Probable Cause: stitching of wound, inadequate wound toilet, bite in dangerous zone of the face. RIG may not be properly administered in all wounds with high viral load, patient although received D14 dose of vaccination.

Results

Table 1: Age wise distribution of patient

Age group	No. of Rabies Cases	Percentage
Upto 15 years	6	60%
16 years and above	4	40%

Table 2: Incubation period of PEP failure cases

Period	No. of Rabies Cases	Percentage
Up to 10 days	1	10%
11 days to 20 days	4	40%
21 days to 30 days	2	20%
>1 to 3 month	1	10%
7 month	1	10%
20 years	1	10%

Table 3: Site of Bite

Site of Bite	No. of Rabies Cases	Percentage
Face	5	50%
Upper limb	1	10%
Lower limb	1	10%
Hand	2	20%
Both Legs	1	10%

Table 4: Treatment history after Exposure

ARV + RIG	No. of Rabies Cases	Percentage
3 doses	1	10%
4 doses	9	90%

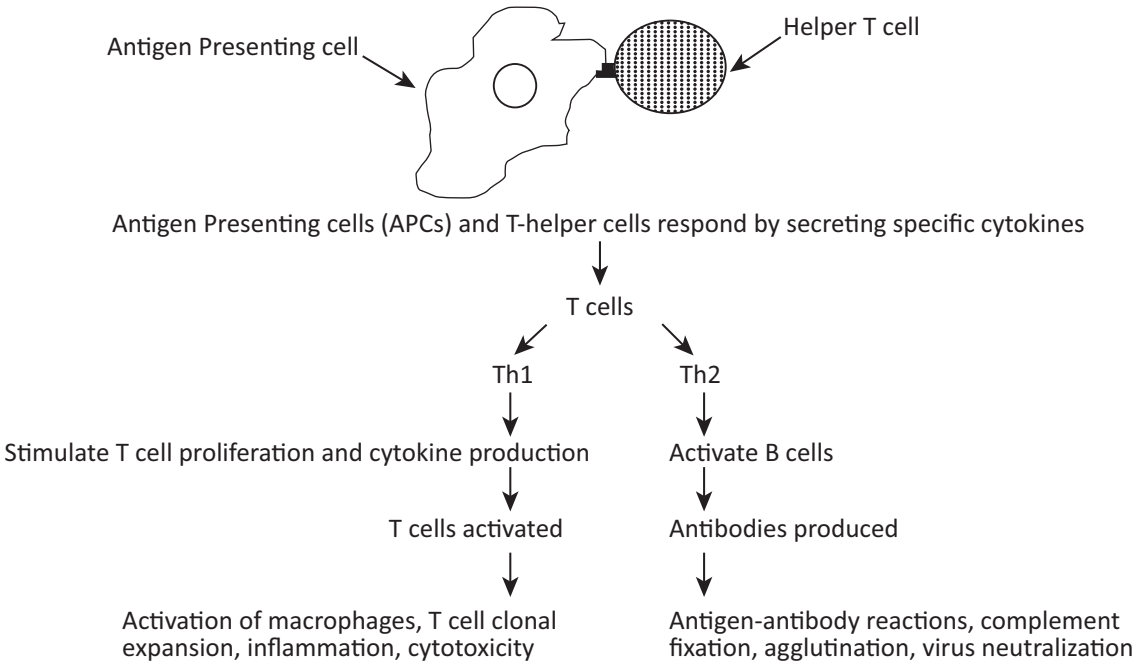
Table 5: Fate of Animal

Animals	No. of Rabies Cases	Percentage
Untraced	4	40%
Not known	4	40%
Killed	2	20%

Discussion:

Considering the failures reported in their article seems to be due to insufficient reactions due to primary response or secondary response. The IgG, IgM antibody detection was not done, due to lack of facilities. It is assumed that, possibly due to poor or no immune response, the patient has not developed adequate primary and secondary immune response. The post exposure treatment failure may be an important factor. Moreover host immune response may not be achieved and immunity was incomplete. Quality and control has to be maintained.

These data were not available during these cases. The viral antigen is mainly proteins or glycoproteins and this is a fact, the immune response to viral antigen is mainly T-cell dependent. The diagnosis in all cases is based on clinical findings only



An overview of the specific immune response

Ref: Immunology, Darla J Wise and Gordon R Carter, 1st Edition, Iowa State University Press, 2004.

Failure during post exposure treatment or following PET is being reported since long time. Most of the cases are not even reported. These cases mentioned above, have been included in the studies. In most of the cases, the treatment protocol has seen some deviations or not technically and scientifically followed.

Viral Load: The possibility of excessive Viral Load during Exposure plays a major role in these cases. In some cases, the authors showed eagerness to point out the fact of high viral load during some of the exposures. Practically it has been observed in some cases that the first bite victim has developed rabies but the rest were not affected even after taking vaccines after 2 months of time. Two patients have reported in Kolkata from Afghanisthan for vaccination after 2 months of exposure (Jamile & Rijaul), where the elder brother who was the first bite victim has developed rabies within few days after bite. Here, Subhajit Mondal, a child has developed rabies within 7 days after exposure in face and anterior chest wall. In spite of administration of RIG and 3 doses of IDRV vaccine soon after 12 hours of bite, in June 2010, after 15 days of exposure, an 8 years old female has also developed rabies (in face) after suspected rabid dog bite. Although the fate of the rest 8-9 persons were not known. There is no method till now by which the viral load can be assessed.

Viral load cannot be assessed as it is neurotrophic virus and not present in the blood.

Wound Wash: The role of wound wash establishes its efficacy as a mandatory initiating procedure. Proper and repeated wound wash with soap and water, under running tap water, has got immense values because the chance of developing rabies seems to be reduced at least 40% to 50%. To be very particular, each wound has to be washed with detergent soap for at least 15 minutes and it has to be established as standard protocol. If a patient is having multiple wounds and in multiple sites, then each site of the different parts of the body will take a lot of time to achieve the goal. The soap is the only media which can wash the outer shell of the glycoprotein, which is responsible for viral attachment. Other application of any other material has got no role except povidone iodine preferably 5% to 10% which is considered as a virucidal agent. Any other application locally like acids etc. causes

development of local burn injury which results more damage of local nerve endings leading to more virus entry very rapidly. Usually the classical protocols in these cases are not possibly maintained. Most of the bites are of category III and especially in the face which is considered as danger zone and more closer to the central nervous system. The wounds, particularly in the face, head, hands, genetalia which is a richly innerved area comes again as a danger zone and the wounds more closure to the central nervous system, directly related with the rate of transmission of virus with a maximum speed per day in the shorter time, which indicates that chance of developing rabies highly increases. These wounds have to be given special care to minimize the chance of treatment related failures.

RIG Application: In the second phase, where RIG application is necessary should be infiltrated as soon as wound wash is completed. RIG infiltrations should be more methodical, scientific and technically accurate. The main objective is that, it neutralizes the virus at the site of entry. To achieve the best results, it should be done immediately after the wound toilet.

There is no role of RIG infiltration intramuscularly because it is a neuro tropic virus and no virus sets in the muscles far away from bite site. If no virus is there, the IM administration is considered as simply misuse and increases the chance of antigen antibody reaction. With this concept, both the authors have never injected rabies immunoglobulin intramuscularly. The correct method of RIG administration is infiltration in the wounds with a minimum prick because multiple prick increases chances of more viral entry through these ports. It should be assured simultaneously that each site has to be infiltrated 100% without leaving a single wound untouched. In the above mentioned few cases, three were reported in primary closure of wound after RIG infiltration. It is practically difficult to access the accuracy of RIG infiltration. The primary closure of wounds with stitches invites creating many viral ports and accumulation of collection inside the wound itself which cannot come outside and increases the risk of viral transmission. This viral transmission rapidly increases the chance of development of rabies and the antibody production is becoming delayed and risky. During RIG application, it should be approached through the base of the wound and it should be kept in the mind that the RIG infiltration will help usually upto day 7 only. These are all included as a part of passive immunization. Delay in administering RIG is also an attributing/ aggravating factor. The RIG infiltration has to be very methodical so that not a single small point in a transdermal wound would be missed during the course of infiltration. The ideal and safe aspect of suturing the wound should take at least 2 weeks of time and the wounds with non infiltration with RIG, should be sutured until it heals from wound or may be attempted for suture if the antibody level reaches its protective value / reaching 100% of seroconversion value.

IDRV procedure: The next important aspect is active immunization which also should be started after RIG administration, taking at least one hour time later, because of avoidance of immediate antibody and antigen reaction.

In case of Subhajit Mondal, possibility of failure in IDRV technique may be inaccurate. There are still chances of Subcutaneous administration in place of Intradermal vaccine administration.

In 60% of patients, the first symptoms were observed within 20 days of exposure and this short incubation may be explained by the severe bite on the face, head and hand which are richly innerved area. All cases present with hydrophobia, with features of a 'furious' form, these features made the diagnosis of rabies easy. In all cases, PEP was started as per usual standard guidelines. No case report for development of paralytic form of rabies was reported.

All the patients received first (D0), second (D3) & third (D7) dose of rabies vaccine in deltoid region. RIG was infiltrated in and around the wound and the rest intramuscularly. In 3 cases, the bite wound was sutured on the same day after RIG infiltration. All cases appeared to have received PEP timely and appropriately, yet died of rabies.

Conclusion:

From the above discussion it can be said that most common probable causes for the failure of PEP were - washing of the wound was not done with soap and water, the wound on the face and hand which are zones richly innerved may be explaining the failure in prophylaxis, delay in RIG infiltration, RIG was infiltrated ½ in the wound and rest ½ in gluteal region, wounds sutured on the same day after RIG infiltration, errors in management and a small transdermal puncture wound may have been missed and possibly not irrigated properly and not injected with RIG, inappropriate intradermal vaccination specially in children is also a great factor.

Two cases of reported late incubation period i.e. one case of 7 months and another was 20 years. In these cases Rabies virus was present in dormant stage.

Death in rabies is inevitable. A current treatment protocol which has been proposed aims only preventive aspect. The quality of vaccine has to be assessed properly and special emphasis has to be given for maintenance of cold chain in the vaccine and rabies immunoglobulin storage. The development of much more immunogenic vaccine and rabies immunoglobulin are required. The quality of vaccine has to be maintained. Only then we can dream for dog mediated rabies free India by 2030. We should have a definite vision to convert the dream into reality. It is the high time to detect underlying cause and to adopt pre exposure prophylaxis by which a definitive role can be played and author's recommendation is also to incorporate in national immunization schedule for pre exposure prophylaxis.

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