Rabies - An Update

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ABSTRACT

The principle of approach to rabies has not changed, but there has been significant modification, more so in diagnosis and prophylaxis with better understanding of modes of transmission of disease, incubation period and knowledge of chronic excretors of rabies virus. Bat-transmitted rabies, graft rabies and rabies by inhalation are well-known entities now. New bat-transmitted *Lyssaviruses* (rabies-related viruses) have been implicated in causation of rabies in UK and Australia, countries considered to be free of rabies. Bat-transmitted rabies is emerging as a major threat in developed world. Extended incubation period upto 7 years is a startling observation, warranting any unexplained neuropsychiatric manifestation in an endemic area to be investigated for rabies. Dogs outliving victims are being reported. Earlier antemortem diagnosis by RT-PCR test and nuchal skin biopsy are path-breaking advances. Tissue culture vaccines replacing nerve tissue vaccines, even in developing countries including India is heartening news. Possible cheaper alternative to human rabies immunoglobulin (HRIG) in form of a 'cocktail of monoclonal antibodies' is being worked out. Nevertheless, survival in rabies still remains a mirage, with only a handful of recovery notwithstanding permanent neurological sequelae.

INTRODUCTION

Rabies is an ancient disease, which still strikes terror in much of the developing world. Much of the terror derives from the inexorable death that follows after the development of symptoms and the long incubation period that leaves dangling the risk of rabies for months and even years. The principle of approach to rabies has not changed, but there has been significant modification, more so in diagnosis and prophylaxis with better understanding of disease. Survival in rabies still remains a mirage, with only a handful of recovery notwithstanding permanent neurological sequelae.[1]

MODES OF TRANSMISSION

Though dog bite is the commonest mode of transmission, there are various other modes of transmission of rabies.[2] (Fig. 1)

Incubation Period

Generally: 20-60 days[15]

Range: 7 days – 1 year

Uncommonly:

i. Minimum 5 days[15]

ii. Maximum upto 7 years[15] (Extended incubation period): 11 months to 6 years of incubation period reported amongthree immigrants to USA[16]

Carrier State in Animals

Dog outliving man: Some reports are there in India[17,18]

Chronic carrier state in animals:[1]

- Observed in healthy vector species e.g. mongoose, skunks, raccoon, fox, jackal
- Bats: observed among vampire, insectivorous and fruit-bats
- Domestic dogs (among those in Ethiopia and rarely in India: *one chronic excretor of virus in saliva for 30 months reported from India[18])*
- Oulou fato: a type of dog rabies with virus of low pathogenicity: prolonged survival of dog occurs (observed in SubSaharan Africa)

CLINICAL FEATURES

Encephalitic and paralytic types of presentation:

Encephalitic form (furious rabies): Classical presentation of hydrophobia with or without aerophobia / photophobia (in absence of coma at onset)

Bite-related:

Animals
- Domestic (Urban rabies): Dogs (in 99% cases in India)[2] Cats (not usually reported from India)
- Other canine animals of forests (sylvan rabies): foxes, jackals, wolves etc.
- Big rodents (occasionally)

Bats
- Vampire – Latin America
- Insectivorous – U.S.A (main mode of transmission of rabies now)

Non-bite transmission:

Inhalation (aerosol)
- Bat-infested caves[3,4]
- Laboratories dealing with rabies virus[3,6]

Oral:
- Mother-to-baby by breast feeding (one report)[7]
- Rabid cow milk (possible, but averted by drinking boiled milk)[8]

Human-to-human
- Graft rabies: Corneal transplant (about a dozen cases reported including those from India, since 1st report in 1979)[2,9,10]
- Exposure to saliva, body fluid of patient (bite or non-bite, sexual) - possible but extremely rare (one child-to-parent case reported by bite)[11]
- Transplacental (one report)[12]

Cryptogenic: No obvious history of exposure**:** trivial bat bite / forgotten animal bite / contact on mucous membrane without an evident bite[2,13,14]

**The information given should be taken in proper perspective to avoid undue panic*

Fig. 1 : Modes of Transmission: Bite or non-bite

Paralytic form (dumb rabies): Presents with flaccid paralysis, observed in about 21% of cases of rabies,[19] possibly due to variation in strain, also observed in partially vaccinated persons and in bat-transmitted rabies, has comparatively longer survival (all survivors of rabies had paralytic type of rabies).[19]

Atypical manifestations

- Rabies without hydrophobia: seen in 23.4% of cases in one series[20] (hydrophobia a feature of furious rabies only)
- Severe itching and excoriation of skin at site of bite: multiplication of virus in corresponding dorsal root ganglion is considered to be the cause[19] (mild itching with paraesthesia, low fever and malaise the usual prodromal features)
- Priapism[21] } Results from viral destruction of the limbic system of brain,

Table 1: Diagnosis[1]

Antemortem		
Specimen	**Aim**	**Test**
Nuchal skin punch biopsy	Antigen detection Viral RNA	IFA* test RT-PCR**
Saliva, tears, CSF	Virus isolation	Tissue culture Suckling mouse inoculation
	Viral RNA	RT-PCR
Serum	Antibody detection	Positive by 2nd week
CSF	Antibody detection	
Postmortem		
Brain	Antigen detection	IFA test
Brain biopsy	Viral RNA	RT-PCR
	Virus isolation	Tissue culture Suckling mouse inoculation
	Viral inclusion body	Negri body (not reliable-false negative and false positive found)

*IFA - Immunofluorescent antibody

** RT-PCR – Reverse transcriptase PCR

Corneal smear testing not recommended: unreliable result, mostly false-negative but false-positive also observed.

- Increased libido — one responsible for normal sex behaviour[19]
- Neuropsychiatric manifestation:
  - subtle seizure[1]
  - catatonic stupor[22]

  In a patient with acute neuropsychiatric illness, a history of bite by a dog (or bat in bat-endemic areas) should raise a possibility of rabies. Bat bite is usually trivial and puncture mark goes unnoticed.[1]
- Non-neurologic manifestations: Observed in prolonged survivors following intensive care treatment[23]
  - Fluctuation of BP
  - Myocarditis - arrhythmia, heart block
  - Diabetes insipidus
  - Poikilothermia

Diagnosis[1] (Table 1)

Earlier antemortem diagnosis is possible due to newer techniques now available.

The diagnosis can be made by following tests:

i. Early identification of Antigen: Immunofluoroscent antibody (IFA) test

ii. Detection of Viral RNA: Reverse transcriptase PCR (RT-PCR) test

iii. Virus isolation:
- Tissue culture
- Suckling mouse inoculation test

iv. Antibody detection (in unvaccinated person)

In one study, RT-PCR test for viral RNA detection from saliva, and brain biopsy for viral antigen detection, was found to be positive in 100% cases.[15] Nuchal skin biopsy for viral antigen was positive in 67% cases.

Table 2: Tissue Culture Vaccines Currently Available in India[25]

First generation:
Human diploid cell vaccine (HDCV) – One dose: 1 ml (IM)*, 0.1 ml (ID)**
Second generation:
Purified chick embryo cell vaccine (PCECV) - One dose: 1 ml (IM), 0.1 ml (ID)
Purified vero cell rabies vaccine (PVRV) – One dose: 0.5 ml (IM), 0.1 ml (ID)

*IM - Intramuscular **ID - Intradermal

PROPHYLAXIS

Animal prophylaxis

There is a current WHO initiative in Asia in this regard. Rabies in stray dogs can be reduced by vaccination, fertility control and clearing rubbish to reduce food supply. [24]

Vaccination of wildlife vectors with oral live attenuated rabies virus or vaccinia-recombinant vaccines has virtually eliminated fox rabies in West Europe.[1]

Human prophylaxis: (Tables 2, 3)

I. Pre-exposure prophylaxis: Indicated for high risk persons

II. Post-exposure prophylaxis:

Optimal prophylaxis consists of the following.

i. Thorough local cleansing of wound with soap and water
ii. Active immunization
iii. Administration of rabies immunoglobulin (RIG), as and when indicated

Tissue culture vaccine (TCV) has almost replaced nerve tissue vaccine for inducing active immunization (Table 2).

Intradermal recommendation by WHO is a newer attempt to have effective antibody titre against rabies with a lower total requirement of vaccine. The principles that allow intradermal vaccination are the better response to an equal volume of antigen when placed in contact with Langerhan's cells of the epidermis and use of multiple sites of vaccination to obtain maximum drainage of antigen-presenting cells to lymph nodes. The intradermal regimens have had remarkable success in Thailand. However, some expertise is necessary for correct intradermal administration.[15, 26]

Human RIG (20 IU/kg of body weight) is prohibitively costly. A 'cocktail of monoclonal antibodies' already being investigated could begin to address the crisis in global supply of RIG and the expenditure involved in procuring it.[1, 27]

Vaccine failure:[15]

Needless to say, it should be viewed seriously, since vaccine failure means certain death. Common causes of vaccine failure are as below.

i. Late starting of prophylaxis
ii. Insufficient cleaning of wound

Table 3: Regimens for pre- and post-exposure vaccination[15]

Vaccination, route	Day (one dose given)*
Preexposure:	
IM	0, 7, & 21 (or 28)
ID	0, 7, & 21 (or 28)
Postexposure:	
IM	0, 3, 7, 14 and 28
ID**	0 (8 doses), 7 (4 doses), 28 and 90
Reexposure (Booster dose):	
IM	0 & 3
ID	0 & 3

* Multiple doses given, where specified

** Used with HDCV, PCECV only

iii. Omission of RIG in severe cases of dog-bite like on face, head and neck
iv. Failure to inject RIG into all wound sites (latest recommendation is to inject maximum RIG locally, not 50% of total as earlier practiced)
v. Suturing of wounds (should be avoided till after 24-48 hours of bite and done only after RIG infiltration locally)
vi. TCV injected in gluteal region (ideal deltoid region in adults and anterolateral thigh in children, in view of erratic absorption from gluteal region)
vii. Concomitant use of immunosuppressants like chloroquine/ prednisolone (warrants doubling of 1st dose of TCV; intradermal administration of TCV may also result in treatment failure in such situation)

MANAGEMENT OF CLINICAL RABIES[15, 28]

To date, there are only five survivors of rabies, including a six year old girl from India.[1] All of them had received some rabies vaccine before the onset of illness and all had paralytic rabies. All, except one, had residual neurologic deficit. Three had profound neurological sequelae i.e., had "limited survival".[1] The approach to management of rabies should be palliative. In unusual circumstance, if a patient has arrived early, a decision may be made to use an aggressive approach. No single therapeutic agent is likely to be effective. A combination of rabies vaccine, RIG, monoclonal antibodies, ribavarin, interferon-α and ketamine (anaesthetic drug which has been demonstrated to inhibit in-vitro replication of virus) may be tried.[23,28] Corticosteroids should not be used. Relatives should be clearly made aware that intensive care treatment may only prolong life; there should be no expectation of survival in unvaccinated patient, and previously immunized patient may have "limited survival", if recovers.[1]

EPIDEMIOLOGICAL ISSUES[1]

Principal animal vectors of rabies virus in various countries are given in Table 4.

Rabies virus is only one of a number of lyssaviruses enzootic in bats. Rabies virus, a single stranded RNA virus was the first of seven lyssavirus genotypes to be identified.

Two newly discovered lyssaviruses (rabies-related viruses) have been identified in Australia (Australian bat lyssavirus [ABLV]) and United Kingdom (European bat lyssavirus [EBLV]),

Table 4 : Principal Animal Vectors of Rabies

Country*	Host
India	Dog
USA	Insectivorous bat
Europe	Fox
Latin America	Vampire bat

* Rabies-free countries - UK, Japan, Antarctica, Australia & New Zealand (Australasia)

countries considered to be free of rabies. Insectivorous bat is responsible for recent reports of rabies in both the countries, by above-mentioned rabies-related viruses (RRV). Disease caused by these viruses has no distinctive feature (furious, paralytic and atypical features all reported).[1] Fortunately conventional post-exposure prophylaxis with TCV is also found effective against these viruses.[15] Oral vaccination of foxes has controlled rabies in West Europe; but bat rabies has emerged as a newer problem in developed world and there is no way bats can be vaccinated.

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