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 days15
Range: 7 days – 1 year
Uncommonly:

i. Minimum 5 days15
ii. Maximum upto 7 years15 (Extended incubation period): 11 months to 6 years of incubation period reported among three immigrants to USA16

Carrier State in Animals

Dog outliving man: Some reports are there in India17,18
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 India19)
- 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)
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**Bite-related:**
- 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)
- Vampire – Latin America
  - Insectivorous – U.S.A (main mode of transmission of rabies now)

**Non-bite transmission:**
- Bat-infested caves\(^3,4\)
- Inhalation (aerosol)
  - Laboratories dealing with rabies virus\(^5,6\)
- Oral:
  - Mother-to-baby by breast feeding (one report)\(^7\)
  - Rabid cow milk (possible, but averted by drinking boiled milk)\(^8\)
- Graft rabies: Corneal transplant (about a dozen cases reported including those from India, since 1st report in 1979)\(^2,9,10\)

**Human-to-human**
- 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 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\(^1\)**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Aim</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuchal skin punch biopsy</td>
<td>Antigen detection</td>
<td>IFA* test</td>
</tr>
<tr>
<td>Saliva, tears, CSF</td>
<td>Virus isolation</td>
<td>Tissue culture</td>
</tr>
<tr>
<td>Serum</td>
<td>Antibody detection</td>
<td>Positive by 2^{nd} week</td>
</tr>
<tr>
<td>CSF</td>
<td>Antibody detection</td>
<td></td>
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</tbody>
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Postmortem

- Brain
  - Antigen detection | IFA test
  - Viral RNA | RT-PCR
  - Virus isolation | Tissue culture
  - Viral inclusion body | Suckling mouse inoculation

**Antemortem**

- Fluctuation of BP
- Myocarditis - arrhythmia, heart block
- Diabetes insipidus
- Poikilothermia

**Diagnosis\(^1\)**

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

The diagnosis can be made by following tests:

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

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

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

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.
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

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**PROPHYLAXIS**

**Animal prophylaxis**

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**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 neurologic 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]),
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). Fortunately conventional post-exposure prophylaxis with TCV is also found effective against these viruses. 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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REFERENCES