ABSTRACT

Rabies is a fatal disease caused by rabies virus, a neurotropic virus and a prototype of Lyssavirus of Rhabdoviridae family. It is transmitted to human beings through infected saliva of dogs and cats during bite. Dog is the cause of more than 90% of human rabies in India. The incubation period is 4-8 weeks (but it may vary from 5 days to 7 years). There are two clinical types of rabies – encephalitic (furious) and paralytic (dumb) types. In the encephalitic (furious) form, the principal malfunction is in the brain stem and limbic system. Patient has hydrophobia in the full-blown form, but the mind remains clear till the end. Death occurs within a week after the onset of symptoms. Paralytic rabies resembles Guillain–Barre syndrome. Diagnosis is mostly clinical. However, direct fluorescent antibody test is used to identify the antigen in skin biopsy from the nape of neck. In the postmortem specimen, demonstration of Negri bodies in the brain confirms the diagnosis. Anti-rabies vaccine is used for pre- and post-exposure prophylaxis. The commonly used intramuscular (IM) regimen is being superseded by intradermal (ID) vaccine because it makes the treatment economical. Whereas touching of animal or lick on intact skin does not require vaccination, any transdermal bite with bleeding requires immediate administration of rabies immunoglobulin (RIG) and simultaneous vaccination with a tissue culture vaccine (TCV). Minor abrasion without bleeding may require only vaccination and no RIG. Rabies human monoclonal antibody (RMAb) is the newest entry in the prophylaxis of rabies which may ultimately replace RIG. Prognosis is grave since there are just six reports of survivors. Treatment is mainly palliative with heavy sedation and/or therapeutic coma (Milwaukee protocol).

Key words: Intradermal vaccine, intramuscular vaccine, post-exposure prophylaxis, pre-exposure prophylaxis, rabies

INTRODUCTION

Rabies is a fatal disease of nearly worldwide distribution that is caused by a filterable neurotropic virus present in the saliva of the infected animals and transmitted to humans through their infected saliva.

Urban rabies is propagated chiefly by unimmunized domestic or street dogs and cats. Street virus is the natural virus present in rabid animals. Wild-life or sylvatic-type rabies is propagated by wolves, foxes, skunks, jackals, etc., which are the main reservoirs and transmitters of rabies. These animals maintain a cycle among them and transmit the disease to dogs and domestic animals. Humans may contract rabies by intrusion into the wild-life cycle of rabies. Bat rabies occurs in certain Latin American countries where the vampire bat serves as an important host and vector for rabies. In the USA, insectivorous bats and wild animals are the most important vectors at present.

The source of infection in humans is the saliva of rabid animals. Domestic dog is the cause of more than 90% of human rabies in India. Dogs also infect cats and other domestic species.

Rabies-free countries are Australia, New Zealand, Japan, Taiwan, Hong Kong, Singapore, Fiji, UK, Ireland, Norway, Sweden, Jamaica, and Barbados. In India, the islands of Andaman and Lakshadweep are rabies free.
EPIDEMIOLOGY

The true incidence is unknown. In India, the estimated mortality is 25,000 to 50,000 deaths per year. Recent figures in China show less than 1000 cases per year. Recent figures in India show less than 1000 cases per year. In Bangladesh, about 2000 deaths and in Nepal, about 200 deaths occur per year. Only 0.01% cases of human rabies occur in the temperate zones.

AETIOPATHOGENESIS

Rabies virus is the prototype of the genus Lyssavirus of the large family of Rhabdoviridae. It is a bullet-shaped virus containing a single-strand of ribonucleic acid (RNA) combined with nucleoprotein that forms a helical coil. The virus is rapidly inactivated by heat. At 56°C, the half-life is less than 1 min. The lipid coat is disrupted by 1% soap solution.

Humans are infected by inoculation of virus-laden saliva by the bite of a rabid dog or animal. Licking on abraded skin or mucus membrane may also result in infection. Scratching by claws can also cause infection. The virus cannot enter through intact skin.

The rabies virus travels in the nerves and is carried centripetally by the flow of axoplasm to the dorsal root ganglion. It multiplies further in the dorsal root ganglion and causes characteristic prodromal symptoms and paresthesias at the site of inoculation. From there it travels to the brain, where massive viral replication occurs. Then the virus migrates along the efferent nerves to almost every organ such as adrenal medulla, cornea, pancreas, nerve twiglet of the hair follicle, and salivary gland, and this leads to virus shedding in the saliva. Virus may also be shed in milk and urine.

At autopsy, widespread infection is usually found in the brain, particularly in the brainstem, hippocampus, and basal ganglia. Congestion of blood vessels of the central nervous system (CNS) and petechial hemmorhages of the pia-arachnoid are found. Histological examination shows perivascular cellular infiltration of lymph spaces. Negri bodies can be detected within the cytoplasm of nerve cells as round or oval eosinophilic inclusion bodies, particularly in the hippocampus and Purkinje cells of the cerebellum. Negri bodies are also found in the brain of more than 95% of rabid animals.[1]

CLINICAL FEATURES

Incubation period is usually 4-8 weeks, but may vary from 5 days to 7 years. Face, neck, and head bites which are close to the CNS have a shorter incubation period.

It may be of two types:
- Encephalitic type (furious rabies) — observed in the majority of cases
- Paralytic type (dumb rabies) — observed in about 20% of cases

Encephalitic type (furious rabies)
The onset is usually sudden. But prodromal symptoms are noted for 2-3 days before the hydrophobic syndrome appears. Only a proportion of people bitten by a rabid animal develop the disease, but once manifested, the disease is almost invariably fatal. Specific prodromal features include paresthesias and itching over the healed bite wound scar. Other features are fever, headache, tachycardia, anxiety, insomnia, restlessness, and myalgias. After 2-3 days, the stage of excitement supervenes. There is mental excitement, restlessness, hyperesthesia, and hydrophobia. Hydrophobia consists of sudden spasm of muscles of the mouth, pharynx, larynx, and the whole of the respiratory musculature, particularly the diaphragm and muscles of inspiration. The attack can be induced by offering water to patients. As the glass of water approaches the mouth, typical spasmodic jerks with violent contraction of diaphragm and other inspiratory muscles occur and water is ejected from the mouth. Afterward, the sight and even the sound of water may provoke the distressing spasm. In the later stage, a wide number of stimuli like sudden sound, strong lights, and even the suggestion of water may induce the attack. Cold air or blowing of air due to fan may also induce an attack (aerophobia). The mind remains clear during the intervals. Hallucinations, delusions accompanied by biting, mania, and spitting may develop later. There is malfunction of brain stem, limbic system, and higher centers.

Death occurs within a week after the onset of symptoms.

Paralytic type (dumb rabies)
It characteristically occurs in bat-transmitted rabies. It also occurs in partially vaccinated persons. Patient presents with flaccid paralysis. It resembles Guillain–Barre syndrome.[1] The stage of excitement is absent. In a few days, paralysis may ascend to involve the respiratory muscles. There is fever and profuse sweating.

The patient has a comparatively longer survival.

DIAGNOSIS

Diagnosis is confirmed by virus isolation, identification of antigen, and detection of antibodies.[1] Virus culture is positive in the first week from saliva, throat swab, eye swab, and cerebrospinal fluid (CSF).
Antigen detection
Direct fluorescent antibody test is used to identify the antigen in skin biopsies taken from the nape of the neck, where hair follicles are highly innervated. It is a sensitive test and positive results are found in 60-100% cases. The corneal smear test is not so sensitive and false-positive results occur.

Antibody detection
Seroconversion occurs during the second week of illness in unvaccinated patients. Antibodies antibody detection in serum and CSF confirms the diagnosis.

Negri body detection
The offending animal is captured (if possible) and humanely killed for demonstration of Negri bodies in the brain. Fluorescent antigen can also be detected in the animal’s brain, and confirms the diagnosis of rabies.

DIFFERENTIAL DIAGNOSIS
This includes other causes of encephalitis or bulbar paralysis (including post-vaccinal encephalomyelitis), Guillain–Barre syndrome, and hysterical pseudorabies.

TREATMENT
Once symptoms develop, only palliative treatment is possible. Seizures should be controlled by heavy sedation. Diazepam 10 mg, six hourly, supplemented by chlorpromazine 50 mg, if necessary, can be used to control seizures. Fluid balance and nutrition must be maintained by intravenous route. Airway and oxygenation should be maintained. On rare occasions, partially immunized patients survive due to extensive intensive care. To date, there are six survivors of rabies including one 6-year-old girl from India, the majority with some neurological deficits like inability to walk and maintain balance. She became the first case of rabies who survived without being vaccinated.

This original Milwaukee protocol has undergone several modifications and out of 25 patients thus treated, only 2 have survived.

PROPHYLAXIS
Rabies vaccine can be used for pre-exposure prophylaxis (PrEP) as well as post-exposure prophylaxis (PEP). The commonly used regimen of intramuscular (IM) administration (1 ml) of vaccine is being superseded by intradermal (ID) vaccination, which requires lesser quantity of vaccine (0.1 ml) and is equally effective.[5]

Post-exposure prophylaxis
PEP is begun immediately after an exposure. Before initiating anti-rabies treatment, one should establish the category of the animal bite [Table 1]. This categorization helps in deciding the future course of action.[8] In addition, tetanus toxoid and proper antibiotics should be used.

PEP consists of a regimen of one dose of immunoglobulin (passive immunization) and five doses of rabies vaccine over a period of 28 days. Vaccines should be given intramuscularly. Alternatively, vaccine can be given intradermally also. Human rabies immunoglobulin (RIG) should be infiltrated around the wound and any remaining portion should be administered intramuscularly, preferably in the gluteal region. Alternatively, equine immunoglobulin 40 IU/kg may

| Table 1: WHO classification of wounds |
|---------------------------------------|
| **Recommended post-exposure prophylaxis category** | **Type of contact with a suspect or confirmed rabid domestic or wild animal, or animal unavailable for testing** | **Type of exposure** | **Recommended post-exposure prophylaxis** |
| I | Touching or feeding of animals | Licks on intact skin | None | None |
| II | Nibbling of uncovered skin | Minor scratches or abrasions without bleeding | Minor | Administer vaccine immediately<sup>6</sup> Stop treatment if animal remains healthy throughout an observation period of 10 days<sup>6</sup> or if animal is proven to be negative for rabies by reliable laboratory using appropriate diagnostic techniques |
| III | Single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva (i.e. licks), exposures to bats<sup>4</sup> | Severe | Administer rabies immunoglobulin and vaccine immediately. Stop treatment if the animal remains healthy throughout an observation period of 10 days |

<sup>4</sup>Exposure to rodents, rabbits, and hares seldom, if ever, requires specific anti-rabies post-exposure prophylaxis, if an apparently healthy dog or cat in or from a low-risk area is placed under observation, the situation may warrant delaying initiation of treatment. This observation period applies only to dogs and cats. Except in the case of threatened or endangered species, other domestic and wild animals suspected as rabid should be humanely killed and their tissues examined for the presence of rabies antigen using appropriate laboratory techniques. Post-exposure prophylaxis should be considered when contact between a human and a bat has occurred unless the exposed person can rule out a bite or scratch or exposure to the mucus membrane.

<sup>6</sup>Exposure to rodents, rabbits, and hares seldom, if ever, requires specific anti-rabies post-exposure prophylaxis, if an apparently healthy dog or cat in or from a low-risk area is placed under observation, the situation may warrant delaying initiation of treatment. This observation period applies only to dogs and cats. Except in the case of threatened or endangered species, other domestic and wild animals suspected as rabid should be humanely killed and their tissues examined for the presence of rabies antigen using appropriate laboratory techniques. Post-exposure prophylaxis should be considered when contact between a human and a bat has occurred unless the exposed person can rule out a bite or scratch or exposure to the mucus membrane.

International Journal of Advanced Medical and Health Research | Volume 1 • Issue 2 • Jul-Dec 2014
be administered. Equine immunoglobulin is cheaper, but the incidence of serum reactions is more.

**IM regimen**

There are currently four types of vaccines available, and the regimen most commonly used in India for IM administration is described below:

**Vaccines**

1. Tissue culture vaccines
   - i. Human diploid cell vaccine (HDCV): One dose – 1 ml (IM)
   - ii. Purified chick embryo cell vaccine (PCECV): One dose – 1 ml (IM)
   - iii. Purified Vero cell rabies vaccine (PVRV): One dose – 0.5 ml (IM)
2. Purified duck embryo vaccine (Vaxirab): One dose – 1 ml (IM)

Regimen: Essen schedule (standard WHO five-dose IM regimen) – The course for PEP should consist of IM administration of five injections on days 0, 3, 7, 14, and 28.

Dose: One IM dose into deltoid

| Day | 0 | 3 | 7 | 14 | 28 |
|-----|---|---|---|----|----|

Human rabies immunoglobulin (20 IU/kg)

The sixth dose is optional and given to individuals who are immune deficient. Day 0 indicates the date of first injection.

Vaccines are ideally given in the deltoid region, and may be given in antero-lateral part of the thigh for children.

**ID regimen**

ID recommendation by WHO is a newer attempt to have effective antibody titers against rabies with a lower total requirement of vaccine. The principle that allows ID vaccination to be effective at a lower dose is that it may be due to the better response to an equal volume of antigen which is placed in contact with Langerhans cells of the epidermis and because of multiple sites of vaccination at the same time to obtain maximum drainage of antigen-presenting cells to the lymph nodes.

On the basis of the recommendations on ID administration of rabies vaccine by WHO and reports of safety, efficacy, and feasibility trials conducted in India, the Drug Controller General of India (DCGI) approved the use of reduced dose ID vaccination in 2006.

The following vaccines are currently approved by DCGI for use by ID route:

**DCGI has recommended the updated Thai Red Cross 2-2-2-0-2 schedule of ID vaccination, which is as follows:**

**ID sites**

| Day | 0 | 3 | 7 | 28 |
|-----|---|---|---|----|
| ID sites | X2 | X2 | X2 | X2 |

This involves injection of only 0.1 ml of reconstituted vaccine per ID site and the vaccination has to be given at two different sites on a single visit (one on each deltoid area, an inch above the insertion of deltoid muscle) on days 0, 3, 7, and 28, using a 1-ml insulin syringe. A bleb formed after injection is a sign of successful ID administration. It is best used in anti-rabies clinics for group vaccinations (for a minimum of 10 persons at a time) because the contents of a broken ampoule of 1 ml have to be used within 8 h and the requirement for a single person on a single visit will be just 0.2 ml and the rest will thus go waste.

ID vaccination is not indicated in patients with immunocompromised states or those on immunosuppressants like chloroquine or prednisolone. They should take full dose of IM injections.

**Wound treatment**

Wound treatment is the most important part of treatment and should begin immediately. It minimizes the viral load. Wound should be thoroughly cleaned with soap and water. Povidone iodine or 70% alcohol should be used to irrigate the wound. Suturing of the wound is to be avoided. Bites of rats, mice, rabbits, and guinea pigs do not require anti-rabies PEP.

**Pre-exposure prophylaxis**

PrEP is recommended for animal handlers and laboratory workers dealing with rabies virus. PrEP consists of three doses of rabies vaccine given either intramuscularly or intradermally on days 0, 7, and 21.

**PROGNOSIS**

The prognosis of rabies encephalomyelitis is grave. At the time of the bite, before the virus has invaded the nervous system, correct and prompt cleansing of the wound and proper post-exposure immunization reduce the risk of development of rabies from 50% to less than 5%. The risk is highest following head bites. Interposition
of clothing, extent of tissue laceration, and immediate local treatment modify the prognosis.

**RECENT ADVANCES**

1. It has been now possible to achieve active immunization with four doses of tissue culture vaccine (instead of five).[6]

2. Fully human monoclonal antibodies (mAbs) have been found to be safer and equally efficacious than conventional RIG.[7,8] Currently, only human and equine polyclonal anti-rabies immunoglobulin (HRIG and ERIG) are available. Replacement of HRIG and ERIG with a safer and more widely available product is recommended. Recently, a combination of two human MAbs, CR57 and CR4098, that has high potential has been identified. A head-to-head comparison between CR57/CR4098 MAb cocktail and HRIG has been made. The MAb cocktail neutralized all viruses from a panel of 26 representative street rabies virus isolates. In combination with the vaccine, the MAb cocktail protected Syrian hamsters against lethal rabies when administered 24 h after exposure, comparable with the results obtained with HRIG. Furthermore, the MAb cocktail did not interfere with rabies vaccine differently from HRIG. These results demonstrated that the human MAb cocktail of CR57 and CR4098 is a safe and efficacious alternative to RIG in rabies PEP.[9]

In a phase 1 trial at the King Edward Memorial Hospital (KEM) in Mumbai, India, 74 healthy volunteers were randomized into several groups that either received rabies human monoclonal antibody (RMAb) or hRIG combined with vaccine. Results showed that the RMAb was well tolerated by all subjects, with no serious side effects. A dose of RMAb produced similar level of rabies virus neutralizing antibody in the blood from volunteers who received RMAb and vaccine as compared to those who received the standard regimen of hRIG and vaccine. Based on these data, Serum Institute of India has received approval to conduct the current trial.[10]

3. Sudarshan et al. have found more compliant “new 1 week ID regimen” equally effective as the conventional 4 week ID regimen. Patients in this trial received PCECV or PVRV at four sites on days 0, 3, and 7 (4-44).[11]

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How to cite this article: Dutta TK. Rabies: An overview. Int J Adv Med Health Res 2014;1:39-44.

Source of Support: Nil, Conflict of Interest: None declared.
Multiple Choice Questions

1. Following countries are rabies-free EXCEPT
   a. Australia
   b. New Zealand
   c. USA
   d. Japan
2. Rabies virus is rapidly inactivated by all of the following EXCEPT
   a. Heat
   b. Soap solution
   c. Plain water
   d. Alcohol
3. In USA, the most important vector for rabies transmission currently is which of the following
   a. Bats
   b. Domestic dog
   c. Domestic cat
   d. Squirrel
4. Rabies is identified by
   a. Guarneri bodies
   b. Negri bodies
   c. Cowdry A bodies
   d. Cowdry B bodies
5. Incubation period for rabies is usually
   a. 48 hours
   b. One week
   c. One month
   d. One year
6. Which out of these is a feature of rabies
   a. Aerophobia
   b. Itching around site of bite
   c. Conjunctival congestion
   d. All of the above
7. Early prophylactic treatment for head and neck bite with bleeding is all of the following EXCEPT
   a. Suturing the wound
   b. Human rabies immunoglobulin
   c. Tissue culture vaccine (TCV)
   d. Tetanus prophylaxis
8. All are features of dumb (paralytic) rabies EXCEPT
   a. May mimic Guillaine Barre syndrome
   b. Patient may rarely survive with ICU management though with sequelae
   c. Patient is violent
   d. Patient usually would have received incomplete rabies prophylaxis
9. Which of the following statements about rabies is UNTRUE
   a. Tissue culture vaccine is better than nerve tissue derived Semple vaccine
   b. Preferred site of inoculation of TCV is gluteal region
   c. Intradermal and intramuscular routes of administration are equally effective in an immunocompetent individual
   d. Human rabies immunoglobulin should be locally infiltrated maximally
10. All of the following about pre-exposure prophylaxis are true EXCEPT
    a. Should be given to high risk animal handlers
    b. Dosage schedule includes three doses on day 0, 7 and 21
    c. Should never be performed with intradermal administration of vaccine
    d. Booster dose should be taken when rabies neutralizing antibody titre falls below 0.5 IU/ml (after testing every two years)

Key to multiple-choice questions
1. c, 2. c, 3. a, 4. b, 5. c, 6. d, 7. a, 8. c, 9. c, 10. c