

Commentary

Rabies : An ancient disease that still prevails

Rabies is an acute and fatal viral encephalitis caused by a single stranded RNA virus belonging to the genus *Lyssavirus* of the family *Rhabdoviridae*. It is one of the oldest disease known to mankind that continues to kill thousands of people every year in spite of the availability of effective vaccines and sera to prevent it. It is primarily a zoonotic disease transmitted to man by the bites from infected animals. It continues to be a major public health problem in India and other developing countries. As per the latest national survey conducted in 2003 about 20,000 people die of rabies every year in India and in more than 95 per cent cases the transmitting vectors are dogs¹. Rabies is also emerging as an important disease in North America as several cases of human rabies have been reported due to exposure to bats². Recently three cases of human rabies after organ transplantation occurred in America; this cautions us that rabies should always be kept in mind in deaths due to non specific neurological illness and diagnosis ruled out by appropriate tests before organ transplantation³. Australia, which was hitherto considered rabies free, has also reported human rabies deaths due to bites from bats⁴. Rabies is present uniformly in all states of India except in Andaman, Nicobar and Lakshadweep islands.

The virus

The rabies virus is a bullet shaped virus measuring about 180 nm in length and 75 nm in width. It is an enveloped virus made up of lipoprotein over which numerous spikes are present. These spikes are made up of glycoprotein, which is necessary for attachment of the virus to receptors and hence determines the virulence of the virus. The other important proteins include the nucleoprotein (N) closely associated with the helical RNA, phospho-protein P, matrix protein

M, and L protein. The rabies genome has about 12,000 nucleotides. The rabies and rabies related viruses are now classified into several genotypes. The strains prevailing in Asian countries belong to genotype I.

Pathogenesis, pathology and laboratory diagnosis

The infection occurs by inoculation of the virus in to the bite wound through the saliva of the infected animals. The receptors for rabies virus include nicotinic acetylcholine receptors, neural cell adhesion molecules (NCAM), and nerve growth factor receptors. There is an initial multiplication of the virus in the local musculature and spread via motor or sensory nerves to the spinal cord and brain. Once virus reaches the brain, there is extensive replication involving every region. Later, centrifugal spread of the virus occurs again through the nerves to non-neural organs such as salivary glands, skin, liver, heart, *etc.* Despite wide-spread replication, there are not many observable pathological changes in the brain except for the presence of Negri bodies. Recent evidence indicates that neuronal apoptosis could play a role in the pathogenesis of the disease⁵; other factors that could contribute to the disease process may be abnormalities in neurotransmitters, accumulation of nitric oxide and pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF- α)⁶. After a prolonged and variable incubation period ranging from few days to few years, rabies presents with two types of clinical manifestations: more common encephalitic form with classical clinical manifestations like hydrophobia, aerophobia and aggressive behaviour and less common paralytic rabies. Laboratory diagnosis may not be required in the first form but paralytic rabies needs laboratory confirmation. Several procedures are available for ante mortem diagnosis *viz.*; immunofluorescence on corneal smear,

skin biopsy, detection of viral antigen in saliva or CSF by ELISA, and recently developed molecular techniques like PCR. However, negative tests do not rule out rabies and confirmation is only by post mortem examination of brain smear by immunofluorescence.

Prevention of human rabies

Though rabies is a 100 per cent fatal disease, it is 100 per cent preventable if state of the art modern prophylactic treatment is instituted soon after the exposure. The WHO has given clear cut guidelines on the categorization of exposures, wound management, active immunization with vaccines and passive immunization with rabies immunoglobulins (RIG)⁷. All these three parameters are equally important. More than a decade ago, in most parts of the world, nerve tissue vaccines have been replaced by highly potent and safe cell culture vaccines like human diploid cell vaccine (HDCV), purified chick embryo cell vaccine (PCEC, Rabipur), and purified vero cell rabies vaccine (PVRV, Verorab). However, in India use of outdated and WHO banned Semple vaccine still continues. It is only recently that efforts have been made by Central Government to phase out this vaccine and replace with modern cell culture vaccines. For full protection, 5 doses of these vaccines are to be administered on days 0, 3, 7, 14 and 28. In all category III exposures, local infiltration of calculated doses of RIG is very essential. Many cases of rabies have occurred despite full course of vaccination but without passive immunization.

In order to economize the administration of cell culture vaccines and to make it more affordable, WHO has advocated abbreviated intradermal (ID) regimens, which saves almost 60 per cent of the cost. These regimens are now routinely followed in Thailand, Philippines and Sri Lanka. Two types of ID regimens are approved by WHO, *viz.*, the 2 site regimen also known as Thai Red cross regimen (TRC, 2-2-2-0-1-1) in which 0.1 ml of vaccine is given ID over deltoids at 2 sites on days 0, 3, and 7 and at one site on days 28 and 90; the multiple site regimen (Oxford regimen) consists of giving 0.1 ml vaccine ID at 8 sites on day 0, at 4 sites on day 7, and at one site on days 28 and 90. Both regimens are effective in producing adequate neutralizing antibody titres. However, these ID regimens are yet to be approved by the Drugs Controller General (DCG) of India but likely to be approved and introduced shortly after the

successful completion of the ongoing feasibility study being conducted by the Indian Council of Medical Research (ICMR).

Newer vaccines that have been developed for animal use include DNA vaccines, Vaccinia recombinant vaccines and modified live virus vaccines for oral vaccination of wild life. Incidence of wild rabies has been significantly reduced in Europe, America and Canada by effective oral vaccination programmes. However, bat rabies poses a significant threat to human population in these areas.

Pre-exposure vaccination is recommended to people at continued risk such as veterinarians, laboratory persons, dogcatchers, forest officials, *etc.* Only cell culture vaccines should be used. The recommended schedule is 1 dose of vaccine intramuscular (im) on days 0, 7 and 28. Pre-exposure vaccination of children in India (at least on voluntary basis) should be encouraged, as these constitute nearly 60 per cent of human rabies deaths. In spite of great advances in virology, there is as yet no treatment for rabies.

Treatment and recovery from rabies

None of the antiviral drugs tested have proven effective though some encouraging results were observed with anesthetic ketamine in experimental animals⁸. Therefore, every effort should be made to prevent this disease after a possible exposure.

Though rabies is considered 100 per cent fatal, well-documented survivals in animals have been reported. So far six cases of human survivors have been reported including one from India⁹ and a recent one from North America¹⁰. All these cases were of paralytic type and diagnosed by indirect evidence of high titres of rabies specific antibodies in CSF but neither virus nor viral antigen was demonstrated. Survival from disease should be considered as a rare possibility in paralytic forms of the disease particularly in pre vaccinated patients when clinical course is prolonged by life sustaining intensive care measures. But most often these heroic efforts have failed to save the lives of rabies patients. Therefore, rabies patients, particularly the encephalitic type, should be isolated, sedated and allowed to die as peacefully as possible.

Conclusions

It is unfortunate that in spite of availability of effective vaccines and sera, rabies takes such a heavy toll of lives in India. In neighbouring countries like Thailand, Sri Lanka and Philippines rabies deaths have been drastically reduced. The latest survey conducted by the Association for Prevention and Control of Rabies in India (APCRI)¹ has revealed startling facts: about 20,000 human deaths annually out of which 89 per cent had not taken post exposure vaccination, children constituting almost 50 per cent, and 17 million animal bites annually out of which only half seek medical advice. This amply speaks of the level of public awareness about this dreaded disease.

There is an urgent need for combined efforts from both medical and veterinary services to evolve strategies not only to prevent human rabies deaths but also to plan future actions to bring down incidence of canine rabies, to reduce and eventually eliminate stray dog population. A National Rabies Control Programme should be able to address this issue.

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