

RABIES: A VETERINARIANS'S CONCERN

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ABSTRACT

Rabies is a zoonosis, affecting domestic and stray dogs, and other wild and domestic animals, in most parts of the world, including Pakistan. The practicing veterinarian has a key role to play in rabies control, in the maintenance of protection in the companion animal populations, in the education of the pet-owning community on rabies, and in the decision-making process that accompanies human exposure to potentially rabid animals. The role encompasses far more than the routine maintenance of health and well-being in pet animal populations. It is important to remain diligent in the immunisation of the people including veterinarians themselves and domestic pets against rabies. Most of the human rabies deaths occur in the tropical developing countries. Diagnosis by clinical signs alone is inadequate since many rabid dogs develop dumb rabies which can easily be overlooked and others die without showing signs of rabies. In addition there are evidences that the animal may recover from clinical rabies and may then intermittently excrete virus in the saliva-this condition is very hazardous, particularly to the individuals like practicing veterinarians as rabies virus may be excreted in the saliva before clinical signs appear and may lead to infection of an unsuspecting and untreated bite victim. In this article current concepts of rabies and its pathogenesis are briefly reviewed with a view to highlight some strategies and guidelines for the practicing veterinarians who must play their role (in addition to their routine responsibility of maintaining health in pet and farm animal populations) to prevent the transmission of rabies virus from the domestic and farm animals to the people including veterinarians themselves who are frequently exposed to these animals.

INTRODUCTION

Rabies ("rage" or "madness" in Latin) has been the object of human fascination, torment, and fear since the disease was recognised in antiquity (Steele and Fernandez, 1991). Rabies, a type of viral encephalitis caused by various strains of neurotropic viruses, mostly belonging to a single serotype in the genus *lyssavirus*, family *Rhabdoviridae*, is almost always fatal (Gill and Shandera, 1995). This virus is transmitted by infected saliva that gains entry into the body by an animal bite or through the broken skin or wound.

Rabies virus is a single-stranded RNA virus, having negative sense and non-segmented genome. The genomic RNA encodes five structural proteins. One of them (matrix protein) is associated with inner side of the viral envelope while another (glycoprotein) forms the spike-like projections on the surface of the virion. The remaining three proteins (transcriptase, nucleoprotein, and phosphoprotein) are associated with genomic RNA (Wunner *et al.*, 1988).

Most wild mammals can become infected with rabies, but susceptibility varies according to species

(Sikes, 1962). Foxes, wolves, and jackals are the most susceptible; skunks, raccoons, bats, bobcats, mongooses, and monkeys are intermediate; and opossums are quite resistant.

Epidemiology and pathogenesis

Dog rabies is still epizootic in the most of the developing countries where dogs are responsible for most human deaths from the disease (Fekadu, 1993). Most of the human rabies cases are attributable to dog bites especially in developing countries where canine rabies is still endemic. The predominance of cases attributable to dogs also reflects the high incidence of dog bites, estimated to be between 200 and 800 per 100, 000 in many countries (Sosin *et al.*, 1992; Swaddiwudhipong *et al.*, 1988; Tuffereau *et al.*, 1985). Rates of human rabies are highest in Asia. More than three cases of rabies per 100, 000 persons per year were reported in India and Sri Lanka in the 1970s, (Bogel and Motschwiller, 1986; Warrell and Warrell, 1988). More than 99% of all human rabies deaths in the world occur in tropical developing countries, e.g., in India alone, 30,000 to 50,000 people may die of rabies each year (Warrell and Warrell, 1995).

Tariq *et al.* (1991) reported a rabies death of butcher who obtained the dead calf that was bitten by a rabid dog, to get the skin of the carcass. This report must be very alarming to Pakistani veterinarians who have to handle not only the domestic pets but also the cattle which are freely exposed to stray dogs particularly in the villages, indicating that rabies may be an occupational hazard not only to practicing veterinarians but also to butchers and those who deal with animal carcasses. Understanding the pathogenesis of rabies (Tsiang; 1993) may lead to new ways to prevent or treat the disease, particularly in Pakistan where stray dogs and most of the pets are not vaccinated. For practicing Pakistani veterinarians, the risk of transmission of the rabies virus other than animal bite should be particularly considered, but fortunately cases of rabies after scratches, abrasions, or the licking of open wounds or mucous membranes are extremely rare (Afshar, 1979), as the risk of rabies after a bite by a rabid animal (5 to 80%) is about 50 times the risk after scratches (0.1 to 1%) (Hattwick, 1974).

Susceptibility to infection is now believed to be dependent upon a number of factors the infecting strain, the host's genetic background, the concentration of nicotinic acetylcholine receptors in skeletal muscle, the size of the inoculum, the degree of innervation of the site of the bite, and its proximity to the central nervous system (Sikes, 1962; Hattwick, 1974; Blancou *et al.*, 1991; Bear *et al.*, 1990). The most unusual feature of rabies is the long and variable incubation period following infection before appearance of overt symptoms. In humans, the incubation period may range from 10 days to many years but is usually 3-7 weeks, depending in part on distance of the wound from central nervous system (Gill and Shandera, 1995). The incubation period in dogs may vary from one week to several months and may be influenced by the site of infection and the virus dose and strain (Fekadu, 1993), thus, head and face wounds usually result in a shorter incubation period than wounds on the extremities, feet, and hands. Fortunately, the virus gains entry into the salivary glands of dogs 5-7 days before their death from rabies (Gill and Shandera, 1995), thus limiting their period of infectivity despite being the carriers for a very prolonged period but it has been also reported that dogs may recover from clinical rabies and may then intermittently excrete this virus in the saliva (Fekadu *et al.*, 1981). In addition, bats present a special problem because they may carry rabies virus while they appear to be healthy, excrete it in saliva, and transmit it to other animals, including other bats, and to humans (Brooks *et al.*, 1991).

After inoculation, a region of glycoprotein attaches to the plasma membrane of cells; a putative binding site is the nicotinic acetylcholine receptor (Lentz *et al.*,

1982). Usually, the virus is amplified in the cells of the skeletal muscles near the site of inoculation for 1 to 4 days (Murphy and Bauer, 1974). When the concentration of the virus is quite sufficient (presenting a possible explanation of the above-mentioned 1-4 days stay at the site of bite), it enters the nervous system through sensory and motor terminals (Murphy, 1977), which is the first step of its journey to the brain. In the peripheral nerves, the virus spreads by retrograde axoplasmic flow at 8 to 20 mm per day until it reaches the spinal cord, when the first specific symptom of the disease (pain or paresthesia at the wound site) may occur (Wilson *et al.*, 1975). Afterwards, as the virus quickly disseminates through the central nervous system, a progressive encephalitis develops, until the virus spreads throughout the body along the peripheral nerves, including those in the salivary glands, where it is shed in the saliva which is the principal route of transmission. Experimental evidence also supports the possibility of virus dissemination to salivary glands by way of bloodstream (Volk *et al.*, 1991).

Clinical features

In humans, history of animal bite with hydrophobia makes the clinical diagnosis of rabies very easy. However, clinically it may be problematic to differentiate rabies from other viral encephalitides (Whitley, 1990). Patients with rabies can have a variety of clinical manifestations (Warrell, 1976; Fishbein, 1991; Anderson *et al.*, 1984). The early symptoms include pain at the site of bite followed by fever, headache, malaise, increased fatigability, anorexia, myalgias, and paresthesias. The skin becomes extremely sensitive even to air currents. Painful laryngeal spasm when he tries to drink water (hydrophobia). Other symptoms of this type of viral encephalitis include muscle spasm, laryngospasm, excessive motor activity, extreme excitability, hallucinations, bizarre aberrations of throat, opisthotonic posturing, and paralysis.

If biting animal seems healthy, it should be kept under observation for about two weeks. If the animal does not die, the sick animal should be killed, to examine its brain for rabies. The pathognomonic lesion of rabies is the Negri body. However, Negri bodies are not demonstrated in at least 20 percent of rabies, hence their absence in brain material does not rule out the diagnosis. In early stage of disease, the fluorescent antibody testing of the skin obtained from the posterior neck may be positive (Gill and Shandera, 1995). As a diagnostic tool, a liquid-phase blocking ELISA (enzyme linked immunosorbent assay) has been developed for the detection and titration of antibodies of principally the nucleoprotein of rabies virus (Esterhuysen *et al.*, 1995). Jayakumar and Padmanaban (1994) of Madras Veterinary College, India have developed a dipstick dot enzyme immunodiagnostic test to detect viral antigens

from brain of rabies-suspected dogs, cattle, horses, cats and goats. On comparison with the direct fluorescent antibody technique (FAT), this test does not show false-positive results and is therefore specific and reliable to detect rabies antigen from the brain tissue of rabies-suspected animals. Antigen-detection ELISA kits for rabies are also available commercially.

Prevention

Rabies is almost always fatal so prevention is the most appropriate approach. In Pakistan and other developing countries, immunisation of pets (cats, dogs, etc.) must be the first step, in addition to the mass campaign to immunise and control stray dogs which may bite humans, and domestic and farm animals. Currently two reliable rabies vaccines are available in many countries i.e human diploid-cell rabies vaccine (HDCV) and rabies vaccine absorbed (RVA). The latter one is Rhesus diploid rabies vaccine (Berlin *et al.*, 1983; Petriciani, 1993). According to the recommendations of the US Immunisation Practices Advisory Committee (1991), these two vaccines are considered equivalent in terms of safety and efficacy. HDCV, the preferable vaccine, is an inactivated whole-virus vaccine prepared from a laboratory strain of rabies virus grown in human diploid cell cultures. Severe untoward local and systemic reactions to HDCV are very rare, so it is very safe, for both pre- and post-exposure active immunisation. However, in Pakistan and many other developing countries, duck embryo vaccine and vaccines derived from the brain tissue of the infected mouse, goat, sheep, rabbit, etc., are also available but they are generally not only less effective but have a high rate of severe toxic reactions and their administration is very complex. For passive post-exposure immunisation, rabies immune globulin (human origin) and equine rabies antiserum are available.

Pre exposure immunisation

Prophylaxis before exposure is of utmost importance for all veterinarians and other persons whose vocational or avocational pursuits put them at risk of frequent unrecognised exposure to rabies. For pre-exposure vaccination, the two immunisation schedules used were those most widely adopted since the first recommendation of HDCV by WHO Expert Committee (1984), either two injections on days 0 and 28 with a booster one year later or three injections on days 0, 7 and 28. Generally, a course of three intramuscular injections of HDCV, (on days 0, 7 and 28), is preferable because a greater and more rapid increase in antibody levels has been reported with the three-injection schedule (mean titre 30.5 IU/ml ranging from 25.5 to 36.6 IU/ml) than the two-injection schedule (mean titre 8.4 IU/ml ranging from 6.6 to

10.7 IU/ml) after 42 days (Dureux *et al.*, 1986). In case of two-injection schedule on 28th day, the neutralising antibody titre has been reported 1.8 IU/ml ranging from 1.4 to 2.3 IU/ml, while in case three-injection schedule this is significantly higher following two injections on day 0 and 7 (means 24.5 IU/ml ranging from 19.4 to 30.9 IU/ml). So a neutralising antibody titre should be checked after 2 week of the last injection (that is on 42nd days after the first injection). Simultaneous administration of chloroquine should be avoided because it diminishes the antibody response to vaccine (Pappaioanou *et al.*, 1986).

Post-exposure immunisation

Local wound therapy should be considered as an important post-exposure preventive measure. The wound should be scrubbed with soap and then flushed with water. **Wounds caused by animal bites should never be sutured.** Treatment with both rabies immune globulin and HDCV (or other vaccine) should be initiated immediately, following the biting by a suspected rabid animal. In USA, no case of failure of post-exposure HDCV has been reported, indicating the efficacy of correct administration of this valuable vaccine, but unfortunately, 13 persons outside the USA have contracted rabies after post-exposure treatment with HDCV, because each of these 13 cases involved some deviation from the recommended protocol (wounds not cleansed, passive immunisation not given, or rabies vaccine injected in the *gluteal rather than the deltoid area*) (Shill *et al.*, 1987; Wilde *et al.*, 1989). Rabies immune globulin of human origin is more preferable than the equine anti-rabies serum. The dose for optimal passive immunisation is 20 IU/Kg (in case of rabies immune globulin, human origin), or 40 IU/Kg (in case of equine rabies antiserum). About 50 % of this dose should be given by local infiltration of the wound, and the rest should be administered intramuscularly into the gluteal region. Equine antiserum should be given after appropriate tests for horse serum sensitivity. **Rabies immune globulin and HDCV should never be given in the same syringe or at the same site.**

For post-exposure active immunisation, WHO recommends five intramuscular (**only in the deltoid muscle**) injection of 1 ml HDCV, on days 0, 3, 7, 14 and 28. However, post-exposure active immunisation for individuals previously given preexposure active immunisation, consists of only two intramuscular injections of HDCV on days 0 and 3.

Conclusion and key message

1. Rabies is almost always fatal, yet effectively preventable.
2. An effective prevention of human rabies, in

- Pakistan and other developing countries, is dependent on the control of canine rabies which can only be achieved by mass-immunisation and control of stray dog populations, in addition to immunisation of domestic animals.
3. There would be an increasing demand for practicing veterinarians to take the lead in the control of this most fearful zoonotic disease. In Pakistan, rabies is an occupational hazard to veterinarians. Hence, preexposure active immunisation is recommended for all veterinarians and others who have frequent exposures to rabies and rabies-suspected animals.
 4. For effective pre- and post-exposure immunisation, WHO recommended doses of vaccines/antisera should be followed to prevent this fatal disease.
 5. In order to prevent the spread of the disease we need veterinary vigilance, the presentation of information about the problem to the pet-owning community and other people who are frequently exposed to animals using all types of mass media. There is a need for co-operation between veterinarians and physicians in controlling rabies and other zoonotic infections.
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