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Canine rabies

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ABSTRACT

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Dog rabies is still epizootic in most countries of Africa, Asia and South America and in these countries dogs are responsible for most human deaths from the disease. 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. 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. Rabies virus may be excreted in the saliva before clinical signs appear and may lead to infection of an unsuspecting and untreated bite victim. Dogs may recover from clinical rabies and may then intermittently excrete virus in the saliva. Prevention of human rabies depends on the control of canine rabies which can only be achieved by mass-immunization and control of stray dog populations.

INTRODUCTION

Wolves, the ancestors of the present-day dog (*Canis familiaris*) were domesticated long before any other wild carnivore species. In the western United States the finding of bones of dogs, which were possibly used for hunting about 8 500 B.C. (MacNeish 1963), is an indication of the early domestication in the New World of dogs as useful pets; dogs may have been the first true pets of man. One of the earliest references to rabies in dogs is from the premosaic Eshnunna code (which predates the code of Hammurabi of ancient Mesopotamia *c.* 4 000 years ago) (Sellers 1954). Today, because of their close association with humans, dogs are considered to be the prototypic animal species for rabies. The natural transmission of dog rabies to humans depends on dogs' relationship with humans and on the density and immune status of the dog population. Dog population density is usually associated with the socio-economic values and habits of a society and whether dogs are primarily reared as pets or for hunting and/or watchdogs, as they are in most countries, or for meat production as they are in some Asian countries (Beran 1982).

In rabies-endemic areas, dogs are responsible for most human exposures and for up to 98 % of human fatalities from rabies. Nevertheless, it appears that human susceptibility to rabies is relatively low. According to earlier data, an average of only 15–20 % of persons bitten by rabid animals (and who received no post-exposure treatment) died of rabies (Balint 1978; Kale 1977). In 1989, 2 499 humans were reported to have died of rabies worldwide (WHO 1992). Dogs were responsible for 93,4 % of the cases where the animal species was known (WHO 1992). Because of the worldwide under-reporting of human rabies, these data are an indication rather than a precise record of dog to human transmission.

Dog rabies is still epizootic in most countries of Africa, Asia and South America. Most African countries report dogs as the main source of rabies, but the total number of reported cases does not reflect

the seriousness of the disease. In Asia, rabies is as poorly reported as it is in Africa and South America and dogs are also recognized as the major vector.

In North America and Europe, where dog rabies has been controlled since the 1960s, rabies occurs mainly in wildlife and dogs account for less than 5 % of all reported cases (Baker 1978; Steck & Wandeler 1980; Wandeler, Budde, Capt, Kappeler & Matter 1988; Krebs, Holman, Hines, Strine, Mandel & Childs 1991). In these areas, canine-rabies control programmes using intensified mass-immunization campaigns and reduction of stray populations, have effectively controlled rabies transmission, especially to humans (Tierkel 1948; Wells 1957; Thongcharoen 1973; Benelmouffok 1978; Fekadu 1982; Belotto 1986). In countries where most stray dogs are unsupervised pets and elimination of such dogs is against certain social values, at least 80 % of the dog population must be vaccinated to control rabies transmission (WHO 1984). Mass vaccination and elimination of stray dogs are the only effective means of canine rabies control.

SUSCEPTIBILITY

In addition to classical rabies, dogs are susceptible to the rabies-related viruses of Lagos bat, Mokola & Duvenhage (Percy, Bhatt, Tignor & Shope 1973; Tignor, Shope, Bhatt & Percy 1973; Foggin 1982; 1983). The dog is more resistant to classical rabies virus than is the fox (Sikes 1962) but less resistant than the opossum (Beamer, Mohr & Barr 1960). Susceptibility has been determined experimentally by the amount of peripherally-injected virus required to cause death. The peripheral lethal dose 50 % (LD_{50}) of rabies virus for dogs varies greatly depending on the strain of virus and age of the animal. In general, dogs under three months of age are more susceptible than adults, but dogs one year and older appear to have equal susceptibility to rabies virus regardless of the strain or size of the inoculum.

Dean, Evans & MacClure (1963) reported that one peripheral dog LD_{50} was approximately equal to 86 000 mouse intracranial lethal dose 50 %; similar values were found using a fox-rabies virus strain (Sikes 1962). However, Fekadu, Chandler & Harrison (1982a) showed that doses of dog street-rabies virus strains as low as 32 $MICLD_{50}$ were lethal to dogs when inoculated intramuscularly.

Experimentally, susceptibility may vary among individual dogs. Some dogs that were inoculated with various doses of a street-rabies virus resisted infection, while others succumbed (Fekadu *et al.* 1982a; Fekadu & Shaddock 1984). Those dogs which resisted experimental street-rabies virus challenge and that did not develop specific neutralizing-antibody during a two-year observation period were re-challenged with a large dose of street-rabies virus, all dogs developed a high neutralizing antibody titer within five days and survived the challenge, while control dogs died (Fekadu & Shaddock 1984). In other instances, some dogs developed ascending paralytic rabies even after vaccination with modified (chicken embryo-adapted low egg passage) live rabies virus vaccine (Pedersen, Emmons, Selcer, Woodie, Holliday & Weiss 1978; Whetstone, Bunn, Emmons & Wiktor 1984).

The mechanism involved in resistance to infection or abortive infection in dogs has not yet been well documented. In mice, cell-mediated immunity plays an important role in rabies infection and is directly correlated with protection against rabies (Iwasaki, Gerhard & Clark 1977; Miller, Morse, Winkelstein & Nathanson 1978; Wiktor 1978; Prabhakar, Fischman & Nathanson 1981; Smith, McClelland, Reid & Baer 1982). In a study of cell-mediated immune response to rabies virus in vaccinated dogs, however, it was shown that both cellular and humoral antibody responses are necessary to adequately protect dogs against rabies virus infection (Gerber, Sharpee, Sweizkowski & Beckenhauer 1985).

INCUBATION PERIOD

The incubation period of rabies in dogs varies from a week to many months. In a report from Great Britain, where six months quarantine is required for imported animals, 50 % of the 26 canine rabies cases reported occurred within one month of the commencement of quarantine, 80 % within four months and the remainder after four months (Waterhouse 1971).

The incubation period apparently depends upon several factors which include the site of exposure (inoculation), the dose and the virus strain. In a study of incubation periods, dogs experimentally infected with various doses of street-rabies viruses to simulate natural infection were observed for at least two years. In the dogs which died of rabies the incubation periods were 7–125 days, depending on the dose and strain used; the incubation periods were inversely proportional to the virus dose (Fekadu 1988). In another experiment, the longest incubation period in an experimentally infected dog was 8,5 months (Tierkel, Koprowski, Black & Gorrie 1949). These findings show that the incubation period is mainly dose dependent, implying that long incubation periods observed in naturally infected animals may be attributable to exposure to very small doses of virus.

CLINICAL SIGNS

The classical course of canine rabies is divided into three phases:

- During the prodromal phase behavioural changes may occur. Aggressive and highly strung dogs may

become friendlier than usual and ordinarily friendly dogs may become shy and seek secluded areas or become snappy and irritable. The temperature may rise slightly, the pupils may dilate and the nictitating membrane may cover the eye. Excessive salivation may occur.

- During the excitative (furious) phase signs of the disease are most easily recognized. The dog becomes severely agitated and restless and sometimes develops the urge to roam. It is most dangerous at this stage because of its urge to bite anything that it encounters. In most cases an altered phonation (a characteristic high pitched bark) develops, caused by paralysis of laryngeal muscles. Spasms and paralysis of the pharyngeal muscles make swallowing difficult and lead to drooling. If the dog does not die during one of the characteristic convulsive seizures the disease usually progresses to muscular incoordination, paralysis, coma and death.
- The paralytic phase (dumb rabies) occurs when the excitative phase is extremely short or absent. The most characteristic sign is the "dropped jaw" caused by paralysis of the masseter muscles. Often, choking sounds as if a bone were stuck in the throat are made and attempts to remove this "bone" have resulted in owners scratching their hands on the dogs' teeth and becoming exposed to the virus.

DIAGNOSIS

The diagnosis of rabies by clinical signs alone is inadequate since some dogs may die without showing any signs of illness while others develop dumb rabies, which can be easily misdiagnosed (Fekadu 1988). In an experiment in which dogs were inoculated intramuscularly with various strains of street-rabies virus, up to 24 % died without showing any signs of illness but were found to be rabid at autopsy; 68–71 % of rabid dogs developed signs of dumb rabies and 6–42 % furious rabies. Furious rabies was rarely observed in dogs that died after a short incubation or morbidity period; the morbidity period lasted up to 14 days and was dose but not strain dependent (Fekadu 1988).

DIFFERENTIAL DIAGNOSIS

The diagnosis of rabies in dogs requires a careful examination of the sick animal and an epidemiological assessment of the disease circumstances. In areas where rabies is endemic, the disease should be suspected in any dog that develops neurological signs. The most important disease in the differential diagnosis is canine distemper, in which signs of encephalitis such as spasmodic chomping, agitation, irritability and epileptiform convulsions may resemble those of rabies. In distemper these signs are periodic in frequency, but in rabies they are progressive and more closely associated with aggressiveness or dropped jaw. Also in distemper (and other forms of encephalitis) compulsive seizures occur intermittently throughout the duration of the disease, whereas in rabies they invariably occur during the terminal (paralytic) stages. Other, but less common diseases that should be considered in Africa include cerebral babesiosis, ehrlichiosis, pesticide and dimazine ("Berenil") poisoning, old dog encephalitis and granulomatous encephalomyelitis (Van der Lugt & Last, unpublished observations).

RECOVERY

Over 100 years ago Pasteur stated unequivocally that dogs may recover from rabies (Pasteur, Chamberland & Roux 1882). Since then, various reports have confirmed that humans and animals may recover completely from either natural or (with animals) experimental rabies (Hattwick, Weis, Stechschulte, Baer & Gregg 1972; Arko, Schneider & Baer 1973; Porras, Bardosa, Fuenzalida, Adaros, Oviedo, Diaz & Furst 1976; Fekadu & Baer 1980; Fekadu, Shaddock, Sanderlin & Baer 1992). However, the concept that rabies is invariably fatal is still widespread. The most common criterion used for a definitive diagnosis of recovery is the presence of high titer virus-neutralizing antibody in the cerebrospinal fluid (Hattwick *et al.* 1972; Porras *et al.* 1976; Fekadu & Baer 1980; Fekadu *et al.* 1992).

Reports of recovery of dogs from natural infection are scanty. One reason may be that, unlike those in experimental rabies, suspect rabid dogs are usually killed immediately and not given a chance to recover. However, of dogs experimentally infected with street-rabies viruses, 0–20 % recovered from clinical rabies without any supportive treatment; recovery was independent of virus strain and dose (Fekadu 1988). In a recent study where dogs were vaccinated with rabies N-protein alone and then challenged with street-virus, five of seven (71 %) were protected in the absence of humoral virus-neutralizing antibody. Three of the five dogs which recovered did so without any supportive treatment. Dogs that were vaccinated with rabies G-protein alone and then challenged with street-virus were either fully protected or died after they developed clinical signs of rabies, indicating that rabies virus-neutralizing antibody alone may not be adequate to fully protect dogs against a high virus challenge (Fekadu *et al.* 1992).

CARRIER STATE

Naturally infected, apparently healthy dogs have been reported to intermittently excrete rabies virus in their saliva (Fekadu 1972; Veeraraghavan 1973).

These observations have been confirmed in experimentally inoculated dogs that recovered without supportive treatment and which then intermittently excreted virus in their saliva for up to 305 days after recovery (Fekadu, Shaddock & Baer 1981). In nature, the excretion of virus in the saliva may thus play a role in the transmission and perpetuation of the disease.

PERIPHERAL DISTRIBUTION OF VIRUS

Rabies virus spreads from the site of infection to the CNS and back to the peripheral organs through the nerves. In dogs experimentally infected with street-rabies virus strains, the ultimate distribution of viral infection depends upon the strain and the dose of inoculum (Fekadu & Shaddock 1984). The amount of antigen demonstrated in tissues also varies markedly, depending on the dose of inoculum. Virtually every organ examined may have viral antigen, confirming previous reports in experimentally infected rodents (Murphy, Harrison, Winn & Bauer 1973; Schneider 1969). Viral antigen has been demonstrated occasionally in most abdominal organs, including the kidneys, intestine and bladder. Virus from the intestinal mucosa, pancreas or liver may possibly be excreted (Fekadu & Shaddock 1984) but would most likely be inactivated by digestive enzymes. The most important source for rabies transmission is the saliva and the oro-nasal secretions: excretion of virus in saliva depends on its presence in the salivary glands.

EXCRETION OF VIRUS

The first proof that saliva is the main vehicle of rabies virus transmission was obtained by Zinke (1804) when he swabbed saliva from a rabid dog on to fresh wounds in other dogs and rabbits. The presence of virus in the saliva may vary in relation to the onset of the disease (Jonnesco & Teodosio 1929; Vaughn, Gerhardt & Newell 1965; Fekadu, Shaddock & Baer 1982b). Rabies virus is usually present in the saliva during the clinical period, but in some studies prior to 1970, it was also demonstrated in the saliva of dogs 3–6 days before clinical signs appeared (Jonnesco & Teodosio 1929; Vaughn *et al.* 1965).

The rate of salivary gland infection in experimentally or naturally infected rabid dogs has been reported to vary from 61–75 % (Vaughn *et al.* 1965; Facade *et al.* 1982b). In an experiment conducted in 1983, however, where ten groups of five dogs were inoculated peripherally with graded doses of canine viruses (to simulate natural dog-to-dog transmission), and were swabbed daily in attempts to isolate virus from the saliva, the presymptomatic excretion time in 37 % of the 39 dogs that succumbed to the disease ranged from 1–14 days; a further 10 % of the dogs which died excreted virus after disease onset (Table 1). At necropsy, 67–83 % of all dogs with positive

Table 1 The relationships between rabies virus strain and dose, salivary gland infection and excretion of virus in saliva

Doses of inoculum (log_{10} MIC-LD_{50}/mℓ)	Virus excretion (Days)		SG[a] titer[b] (log_{10}MIC-LD_{50}/mℓ)	No. of dogs SG/brain positive
	Before onset	After onset		
Ethiopian dog virus				
5,8	–	–	3,2	1/4
4,8	–	–	2,1	1/4
3,8	14	–	6,3	1/3
2,8	5	1; 4	1,0–5,3	4/4
1,8	4; 5	4	3,0; 6,3	2/2
Mexican dog virus				
5,7	1	–	2,2; 2,7	2/5
4,7	1	2	1,0–6,2	4/5
3,7	2; 4	1; 2	4,3; 6,1	4/5
2,7	1; 2; 7	–	1,0–6,7	4/4
1,7	–	–	5,3; 6,4	2/3

[a] SG = salivary gland
[b] Virus titer expressed as log_{10} of mouse intracranial lethal $dose_{50}$/g

salivary glands excreted virus in their saliva before and during illness and 25–100 % of the dogs in each group, depending primarily on the dose of the inoculum, had virus in the salivary glands at death (Tables 2a and b). Almost all the dogs (95–100 %) inoculated with a lower dose (30–300 $MICLD_{50}$) had virus in the salivary glands, while dogs inoculated with high doses rarely did. Only 68 % of the dogs inoculated with virus of Ethiopian origin died, whereas 88 % of those inoculated with virus of Mexican origin died. In summary, this experiment showed that there is a relationship between virus strain and dose and the production of virus in the salivary glands and excretion of virus in the saliva. The canine rabies virus strains used in the experiment described above seem to be excreted long before the onset of disease, unlike the fox or dog strains studied earlier (Vaughn *et al.* 1965).

The onset of virus excretion in the saliva before sickness becomes apparent is crucial, since transmission may unknowingly occur and no preventive measures can be taken because the animal appears normal; the failure to appreciate the significance of apparently normal but infective animals can result in delayed diagnosis with possible fatal consequences in people exposed.

Transmission of rabies from rabid animals to humans usually depends on the presence of virus in the salivary glands but failure to demonstrate virus in the

Table 2a Virus excretion in saliva, in relation to onset, and salivary gland titers of dogs dying after inoculation with Ethiopian dog street-rabies virus

Dose of inoculum (log_{10}MIC LD_{50}/mℓ)	Virus excretion (Days)		SG[a] titer[b] (log_{10}MIC-LD_{50}/g)	No. of positive dogs
	Before onset	After onset		
$10^{5,8}$	–	–	3,2	1/4
$10^{4,8}$	–	–	2,1	1/4
$10^{3,8}$	14	–	6,3	1/3
$10^{2,8}$	5	1; 4	1–5,3	4/4
$10^{1,8}$	5; 4	4	3,0; 6,3	2/2

[a] SG = salivary gland
[b] Virus titer expressed as log_{10} of mouse intracranial lethal $dose_{50}$/g

Table 2b Virus excretion in saliva, in relation to onset, and salivary gland titers of dogs dying after inoculation with Mexican dog street-rabies virus

Dose of inoculum log_{10}(MIC LD_{50}/mℓ)	Virus excretion (Days)		SG[a] titer[b] (log_{10}MIC LD_{50}/g)	No. of positive dogs
	Before onset	After onset		
$10^{5,7}$	1	–	2,2; 2,7[a]	2/5
$10^{4,7}$	1	2	1–6,2	4/5
$10^{3,7}$	2; 4	1; 2	4,3; 6,1	4/5
$10^{2,7}$	1; 2; 7	–	1–6,7	4/4
$10^{1,7}$	–	–	5,3; 6,4	2/3

[a] SG = salivary gland
[b] Virus titer expressed as log_{10} of mouse intracranial lethal $dose_{50}$/g

salivary glands of rabid animals at death does not exclude the possibility of virus having been excreted in the saliva; rabid animals may on rare occasions excrete virus in the saliva, yet have no virus in the salivary gland or brain at death (Lodmell, Bell, Moore & Raymond 1969; Fekadu *et al.* 1982b). Tonsils may play an important role as the sequestration site and source of excreted virus (Fekadu, Shaddock, Chandler & Baer 1983).

Table 3 Site of bite on humans who died of rabies (%)

Bite site	Parish *et al.* 1959	Veeraraghavan 1973	Fekadu 1982
Head and neck	16	11	28
Upper extremity	37	46	41
Lower extremity	47	43	31

DOG BITES IN HUMANS

The importance of the bite site in human rabies cases has been reviewed (Parish, Clark & Frobst 1959; Veeraraghavan 1973; Fekadu 1982) (Table 3). In areas where dog rabies is endemic and is the main source of human rabies, 37–46 % of rabies patients who died were bitten on the upper and 31–43 % on the lower extremities; 11–28 % were bitten on the head or neck. In Ethiopia, where dogs are responsible for most human exposure and rabies-associated death (over 98 % of the 488 humans who died of rabies were bitten by rabid dogs) (Fekadu 1982), 41 % were bitten on the upper extremities and 31 % on the lower; 28 % were bitten on the head or neck. Of these cases, 134 (27 %) occurred in children under ten years of age; 71 % of these were bitten on the head, neck or upper extremities, while only 10 % of the adults were bitten on the head. This may be due at least in part, to the short stature of children (Fekadu 1982).

Dog rabies control

For many centuries rabies has been known as a disease primarily transmitted from dogs to humans; this is best explained by the close relationship between humans and companion animals. Dogs still serve as the principal vector species in most parts of the world (WHO 1992), although reliable prevalence data are sometimes non-existent because of poor reporting. The information collected annually by the WHO on the worldwide status of rabies from rabies-endemic countries (in the annual WHO questionnaire responses) by no means reflects the actual morbidity and mortality caused by rabies. For example, in the WHO report for 1989 from India, 288 cases of human rabies were reported, but in a recent report it was stated that "rabies accounts for 25 000–50 000 deaths every year". The actual figure is thought to be double—in Dehli alone over 300 rabies deaths occur; the overwhelming number of victims being young (1–24 years old) (Sehgal & Bhatia 1985). In Africa, most countries reported dogs as the main source of rabies, but the total number of reported cases does not reflect the seriousness of the disease. In the United States and Europe, however, where rabies reporting is optimal and dog rabies is under control, locally acquired rabies attributable to dogs is rarely reported even though most animal bites inflicted on humans are caused by dogs (Krebs

et al. 1991). Of the few canine rabies cases reported none are caused by dog-to-dog transmission; all are due to spill-over from wildlife reservoirs.

Prevention of human rabies depends therefore on the control of canine rabies; this can only be achieved by mass-vaccination of dogs and control of the stray-dog population.

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