Rabies in Israel 2006: An Update and Review

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Abstract

Rabies continues to be a modern day disease and, until recently, one of the few infectious diseases with 100% fatality rate, despite treatment. This paper will provide a comprehensive review of the history, epidemiology, pathophysiology, and clinical features of rabies. Part of the mission is to understand the changing epidemiology of domestic rabies in the Middle East in recent years. We review the recent dramatic change in the approach to the treatment of clinically overt rabies. A rational approach to the decision-making process for administering post-exposure prophylaxis (PEP) is presented.

MeSH Words: Rabies, Israel, Humans, Animals, Bites, Stings, Disease Transmission, horizontal, Tissue Donors

History

The realization that rabies is a disease transmitted by infected dogs dates back to ancient Greek times. In Aristophanes' Lysistrata there is mention of smoke that is compared to mad dog activity. The word for mad dog is "cognate" with the name of the genus of the rabies virus, *lyssa* [1]. In ancient Rome, rabies was considered to be transmitted by the frenulum of infected dogs. This led to the treatment of clinical rabies by cutting the frenulum of the suspected dog in which the rabies worm was felt to reside, and applying it to the infected victim. In medieval times, the patron saint of rabies and its cure was Saint Hubert of Liège, Belgium. Although some accounts have him making the sign of the cross on the head of a dog or an infected human, he is also said to have used his keys, which were a religious symbol of the cure for rabies, to treat human patients with the disease. Although the keys themselves resided in the shrine at St. Hubert, red-hot irons, intended to represent the keys, were applied to the bite of a rabid dog. Since these hot irons effectively cauterize and neutralize a virus, such treatment was occasionally efficacious. However it was not until Pasteur's treatment of Joseph Meister, a 9 year-old boy bitten by a rabid dog in 1885 that a rational, immunology-

based approach to rabies in humans was discovered [2].

The rabies virus is a member of the Mononegavirales order, viruses with non-segmented, negatively stranded RNA genomes. Within this order, viruses with bullet shapes reside in the Rhabdoviridae family. Lyssa was the female spirit of rage in ancient Greek mythology, thereby giving us our present word for the family of viruses to which the rabies virus belongs, i.e. Lyssavirus.

Epidemiology

The epidemiology of human rabies closely follows that of animal rabies, which is responsible for approximately 50,000 deaths annually worldwide. Most of these deaths result from canine rabies from bites or saliva. Most frequently, the human deaths involve male patients, children under the age of 15 and the elderly.

In the Middle East, rabies is enzootic in urban and sylvatic forms [3-5] (Fig. 1). Although foxes are the main reservoir for sylvatic rabies in Israel, a sophisticated genetic analysis of various animal sources of rabies from 1993–1998 revealed that five variants were related geographically, within four geographic regions, but not by host species. Phylogenetic analysis demonstrated that within each of the four geographical regions (Golan Heights; Galilee; Central-Southern area; Arava Valley) the rabies virus isolates represented more than a single animal species.

Although there were no cases in Israel from 1971 for twenty-five years, in 1996 a soldier in the Golan Heights, apparently bitten by a small rodent on the lip; two civilians died from rabies in 1997 [3,6-8].

Modes of Transmission

Human rabies is the consequence of a person's exposure to the rabies virus, most often via the saliva from a live animal, usually as the result of a bite. Exposure is defined as contact with the rabies virus that has the potential to cause disease in a human. Entry of the virus into the body is usually the consequence of penetration of a person's skin or mucous membranes. Risk of rabies from a bite is approximately 8-10 the times that resulting from a scratch or a lick. This is probably the consequence of the bite representing an inoculation of the rabies virus deeper into the skin and nearer the neuromuscular junction than a mere scratch or lick.

The development of the disease after exposure depends on several factors. These include: severity of the bite, location of the bite, and possibly the virulence of that particular virus. As mentioned above the more severe, i.e. deep and wide, the bite, the more likely the virus will be able to cross the neuromuscular junction. Just as the HIV virus is most successfully transmitted with a large bore syringe and a deep injection, the likelihood of transmission of the rabies virus increases greatly with a deep inoculating bite.

The location of the bite also is important: the closer the bite, and therefore the virus, is to the nervous system – especially the central nervous system – the more likely rabies will ensue. The chances of contracting rabies from a bite to the head, is probably four to 10 times greater than a similar bite to the leg. The possibility that some strains of rabies virus are more virulent than others has been raised in recent years and has been proposed by one author [9] as a possible explanation of the 2004 successful treatment of post-exposure rabies without vaccination (see below).

Non-bite exposure can result from a scratch or the licking of an open wound or mucous membrane. Another form of non-bite exposure may also result from aerosolized rabies virus, e.g., inside a cave with many bats [10], or in the laboratory [11].

Lastly, the transplantation of organs containing viable rabies virus is a very successful vehicle for transmitting rabies. The risk of contracting clinical rabies for humans receiving transplanted organs, including corneas, remains significant [12-14]. In 2004, four U.S. organ transplant recipients from a common donor – three having received solid organs and a fourth, an iliac artery segment [15,16]. Three German organ transplant recipients also died of rabies at about the same time [17].

One hypothesized mechanism of infection is transmission mediated by the olfactory neuro-endothelium. Since very few human rabies

victims interviewed before cognitive decline can recall an exposure to a bat or a rabid animal, there remain a few mysteries about the exact nature of exposure and infection [18].

Pathophysiology

Clinical rabies develops as a result of an exposure to an animal or animal's body part containing rabies virus. Not all exposure leads to disease; asymptomatic infection is possible as noted by the presence of rabies neutralizing antibodies in animals and humans without clinical signs of infection [19]. It is unclear why some persons develop human rabies and others do not. The development of rabies may be a function of the virulence of the particular strain of rabies virus or the role of neutralizing antibodies, killer lymphocytes, interferon, or other immunologic defense mechanisms.

The development of rabies as clinical disease entity is a consequence of the successful cycle of infection replication by the rabies virus in the host organism (figure 1).

The cycle begins with inoculation and attachment of the rabies virus to a nicotinic acetylcholine receptor. The virus may enter the peripheral nervous system immediately if the inoculum is sufficiently large. Usually, however, there is an incubation period of days to months, and rarely years. This incubation is a time during which the rabies virus enjoys an amplification in skeletal muscle cells until it achieves a concentration sufficient to allow infectious units to cross the myoneural junction and enter the nervous system. After the rabies virus enters the nervous system, it is immuno-invisible and no successful PEP is possible. Until 2004 no reasonable hope of treatment, with or without vaccination, was possible either.

Once in the nervous system the rabies virus spreads by retrograde axoplasmic flow at the rate of approximately eight to twenty millimeters day until it reaches the spinal cord. When it does so, the patient often experiences paresthesias, pain or pruritus at the bite site in approximately half the patients. These symptoms are felt to be secondary to virus replicating in the spinal cord. Thence it spreads to the central nervous system spreading by cell-to-cell transfer, axonal transport and by free passage in intracellular spaces at the rate of 200 to 400 mm per day.

A rapidly progressive encephalitis ensues in most patients followed by centrifugal spread of virus along peripheral nerves and tissues out the body. This dissemination through peripheral nerves explains the presence of rabies virus in donor organs in transplantation rabies. The presence of the virus to salivary glands renders saliva infectious and is the rationale for recommending PEP for close human contacts of human rabies virus patients, a theoretical precaution only since no human to human rabies in health-care providers has yet been documented [20-22].

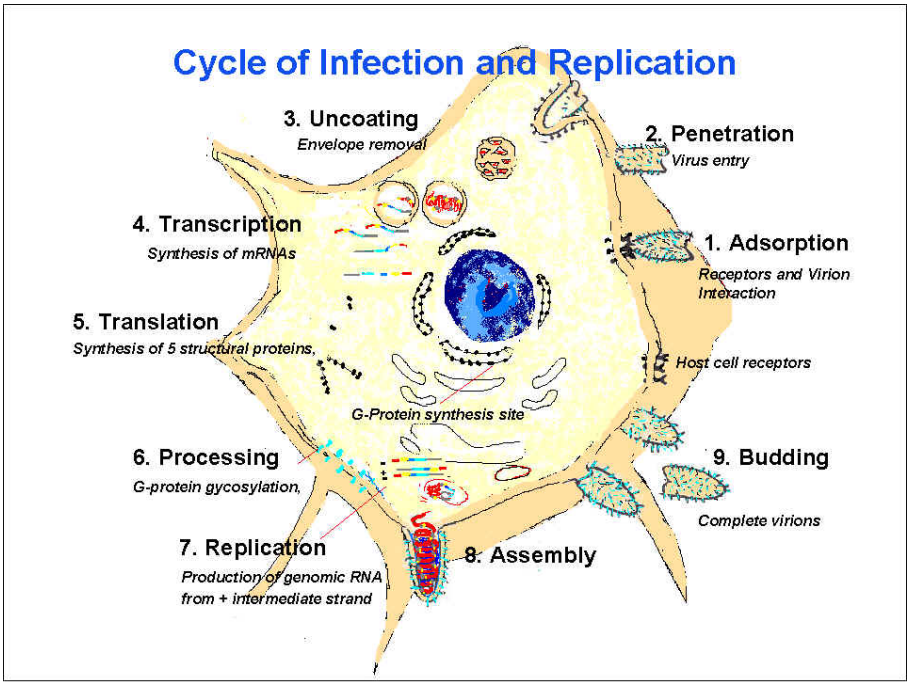
Clinical Presentation

The progression of clinical disease is marked by stages. The incubation phase lasts approximately 31 to 90 days. Incubation is the interval from exposure to first overt symptoms. Although the average incubation lasts from one to three months, it can range from four days to many years [23]. For this reason health care providers should always treat a patient with an exposure to a rabid animal with the entire course of PEP at the first visit, including rabies immune globulin. The incubation period can be shorter in patients who are received bites to the head; deep and extensive bites; bites with proximity to the central nervous system; bites in children; and bites in patients who are immunosuppressed or are receiving steroids.

A prodromal phase heralds the onset of clinical rabies and the end of the period within which one may successfully treat an exposed person with PEP. It consists of nonspecific "viral" symptoms of cough, sore throat, diarrhea, occasionally paresthesias at the bite site, and lasts approximately two to ten days. This signifies the entrance of the virus into the motor end plates and its migration centripetally to the spinal cord. At the end of this period is the acute neurologic stage. At this time there are two distinct clinical manifestations that may occur: the furious and the dumb.

The furious form lasts two to seven days, is more encephalitic and affects about three quarters of patients. It is marked by fluctuating consciousness, with alternating severe agitation and periods of relative normalcy; phobic spasms with the pathognomonic hydrophobia and aerophobia; and autonomic dysfunction (anisocoria, priapism and increased salivation.)

Figure 1: Cycle of Infection and Replication of the Rabies Virus
Ref: http://www.cdc.gov/ncidod/dvrd/rabies/the_virus/virus.htm#top



Hydrophobia is believed to be due to an exaggerated protective respiratory tract reflex and not spasm of the pharynx or larynx. It lasts a few seconds and produces choking and gagging and therefore a fear of water.

The paralytic, or dumb, variety, results in paralysis from involvement of the spinal cord, and lasts slightly longer. Four patterns are possible: most commonly a flaccidity confined to, or most prominent in, the bitten extremity; quadriplegia; a transverse myelitis and an ascending form, simulating the Guillain-Barré syndrome. At the end of either of these two periods coma begins, presaging death in a few days unless the patient is supported in the environs of an intensive care unit. Until recently, death was always the end result of clinical rabies in human patients.

Diagnosis and Differential Diagnosis

The diagnosis of rabies is initially made on clinical evidence. Epidemiologic history may be helpful although approximately a third to a quarter of cases of human rabies do not recall an exposure. Usually the patient presents with an encephalitis of unknown etiolology. The neurologic examination is either normal or nonspecific. The usual chemical hematologic and imaging tasks are useless. Although the patient may have an elevated CSF and or protein and or white blood cell count, the results are nonspecific.

A specific diagnosis can only be made with viral tests. Viral isolation can be positive in the first two weeks of illness but may take up to three weeks to return from specialized centers. Rabies virus-specific and neutralizing antibodies may be positive as early as the sixth day in unvaccinated patients and are usually positive in all patients by day 13 as the rabies virus is very antigenic. Antibodies in the CSF in vaccinated patients are indicative of infection rather than a result of immunization. Fluorescent antibodies in skin biopsies, for example the nape of the neck, are also helpful. In approximately a third of patients the diagnosis is only made post mortem. The serum and vitreous humor can be tested for rabies virus nucleic acid by reverse transcriptase polymerase chain reaction (RT-PCR) analysis. Additionally nucleotide sequence analysis

can be performed for variant identification. A paraffin

block brain tissues can analyze with direct fluorescent antibody test (DFA) and RT-PCR. On a microscopic level histologic examination may show Negri bodies.

Negri bodies are pathognomonic eosinophilic intracytoplasmic inclusion bodies named for Adelchi Negri who discovered this histologic finding in 1903. Also called a Lyssa body, it can be found in the cerebellum, thalamus, hypothalamus and brainstem in approximately three quarters of patients who succumb to rabies.

The differential diagnosis is broad. When confronted with a patient with the furious type of rabies one must consider viral encephalitides such as herpes and arbor virus; allergic encephalitis secondary to nerve tissue derived rabies vaccine; delirium tremens; psychiatric disorders; other infectious diseases such as typhoid, rickettsial disease, tetanus, cerebral malaria, and Creutzfeld-Jacob disease [18]. Although furious rabies may suggest a diagnosis of Creutzfeld-Jacob disease, the former will have fever and an elevated CSF protein whereas the latter will not. Also, the course of furious rabies is too rapid for Creutzfeld-Jacob disease. The differential diagnosis for the paralytic form of rabies includes polio, botulism, simian herpes B encephalitis, and Guillain-Barré syndrome. Some differentiating characteristics in rabies versus Guillain-Barré syndrome are the following in rabies: fever, intact sensory functions; quadriparesis with involvement of proximal muscles, loss of deep tendon reflexes and urinary incontinence; and, lastly, percussion myoedema.

New Hope for the Treatment of Human Rabies

Until the exciting news of the recovery of a young girl from clinical rabies in Wisconsin, USA, early in the year 2004, there was no real hope for arresting the inexorable course of rabies once symptoms had begun in a human being. The story of this landmark case was amply described in the June 16, 2005 issue of the New England Journal of Medicine [24].

After a 15 year-old girl was bitten in church by a bat on her left index finger, she received local care with hydrogen peroxide but no medical attention. One month later, she developed a bilateral sixth nerve palsy and ataxia. At this

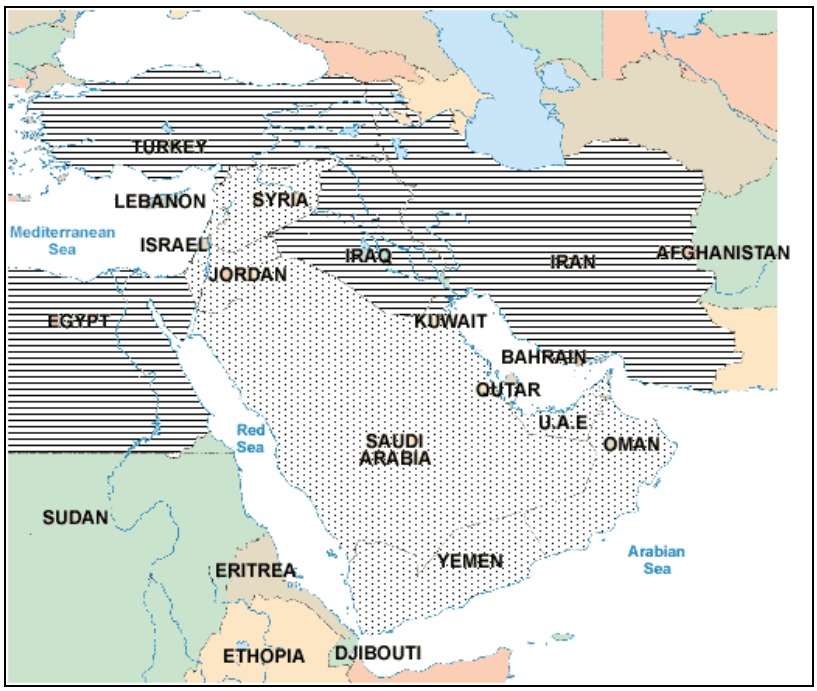
time an MRI and MRA were negative. She was transferred to the Medical College of Wisconsin where another MRI and MRA were again negative. On hospital day number two, her physicians demonstrated the presence of rabies virus specific antibody in her CSF and serum. Her physicians decided to embark on a theoretically rational therapy, albeit one heretofore never tried. Since the rabies virus is not, unlike herpesvirus, neurodestructive but rather disrupts function with excitatory effects leaving cerebral architecture more or less intact; and since humans characteristically effect a vigorous antibody response to rabies virus antigen; and since there was experimental evidence to support the use of anti-rabies medications, they suggested this course of therapy to the family.

After obtaining informed consent from the family the physicians initiated a therapy aimed at maintaining the patient's internal ante morbid milieu, with a combination of anti-excitatory and in vitro antiviral medications, while the patient continued to mount her native immune response. Since the patient already had a measurable antibody response by the time of initiation of their treatement, and since they were fearful of a potentiated immune response, they therefore did not administer human diploid cell vaccine for rabies. Instead, they executed a very carefully constructed blueprint for her care using the following agents: ketamine (for possible anti-rabies effects); midazolam (for anti-excitatory effects); amantadine (for its anti-excitatory and possibly anti-rabies actions); ribavirin (to protect against possible rabies myocarditis); and blood transfusions (to maintain normoxia). The child was intubated and kept on a ventilator until day #32, sedated withmidazolam until day when the IFA in blood/serum attained levels of 1:32000, when it was withdrawn. Thereafter, the patient made steady progress, sitting, speaking. She was discharged on hospital day #76. A video has been placed on the internet to demonstrate her remarkable recovery [25].

Prevention and Treatment

Prevention of rabies is relatively straightforward and consists of a primary strategy aimed at

Figure 2: Animal Rabies in Middle East



horizontal lines = low endemicity
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modified from data in:
http://www.rabies.net/cont_50.risk_areas.php
(Accessed August 7, 2006)

avoiding interactions with possibly rabid animals and, for some persons at greatest and unavoidable risk, primary vaccination; and a secondary defense after an exposure has

occurred. This primary strategy is both personal, i.e, a strategy any individual can effect, and regulatory, i.e., one the state often controls by laws governing importation, ownership of, vaccination of, and sequestration of animals. This first line of defense is dependent on the distribution of rabies in the animals in one's environment and therefore the risk of exposure after an interaction. This risk may be almost zero in areas with no domestic rabies, e.g. Australia, or with strict and well-enforced animal vaccination laws, such as in Israel. The personal strategy involves knowledge of which animals may have rabies, appropriate behavior when near such animals, and knowledge to seek help after an exposure. Governmental laws are generally known to citizens and beyond the scope of this paper. Primary, or pre-exposure, vaccination is described below.

The second line of defense is post-exposure prophylaxis with immune globulin and vaccine and, now, in light of the Wisconsin 2004 experience, a realistic hope of successful treatment ending with a neurologically functioning patient.

The vaccines available for rabies vaccination are the following: HDCV (human diploid cell vaccine); RVA (rabies vaccine adsorbed), and RabAvert. Pre-exposure vaccination consists of three shots for people with a recognizably likely chance of exposure to a rabid animal. This includes those persons involved in the production of the vaccine, veterinarians or animal handlers in areas of enzootic rabies and, lastly, travelers to areas wherein they may come

in contact with rabid animals, usually feral dogs often roaming loose [26].

Primary vaccination, or pre-exposure vaccination, consists of three intramuscular injections of HDCV or RVA in the deltoid days 0, 7 and 21 or 28. Pediatric dosage is the same. Safety of use in pregnancy has not been established. One should beware of administering a primary series to anyone simultaneously receiving steroids or chloroquine since both may suppress the immune response. For patients with continuous or frequent risk, antibody titers should obtained to guide the administration of subsequent booster shots.

Post exposure prophylaxis consists of five shots and is given to those people who may have had an exposure to an animal that reasonably might be rabid. Treatment decision is a function of both the nature of the exposure, the animal type and the location; and lastly the person's vaccination status pre-exposure. Of particular importance is the fact that the duration of time from exposure to seeking medical attention is of no relevance. A valid exposure even a year earlier should still elicit a sincere effort to ascertain the need for post-exposure prophylaxis. Many algorithms exist to guide the health provider's decision-making to offer post exposure prophylaxis or not given the circumstances of the exposure [27-32].

Key elements in deciding whether to give post exposure prophylaxis include the following: Is the animal a type known to be possibly rabid? Where did the exposure take place and what was the provenance of the animal? It is important not to assume that the exposure or the animal is of local origin [21,33].

Next, one must ask: Was the exposure of a type known to transmit rabies? Any close contact wherein the animal's saliva or other infected bodily material has reached the patient's skin or mucous membranes, however trivial the contact, should prompt a serious consideration of offering PEP. Should there be any question regarding the animal, the exposure or the host status (steroids, chloroquine, immunosuppressives, etc.), the primary provider should query local or national resource personnel expert in rabies care.

For post-exposure prophylaxis, the three essential elements consist of a) cleansing the wound locally with 20% soap and water which may reduce the risk of rabies by 90%; b) administering human rabies immune globulin (20 IU/kg for all age groups; half in the bite site if anatomically feasible; and c) vaccination. It is vitally important to administer the vaccine in the deltoid, not the gluteus [34,35].

It is equally essential never to administer human rabies immune globulin and human diploid cell vaccine in the same syringe or at the same site. The recommended schedule for vaccine administration is days 0, 3, 7, 14 and 28. The World Health Organization recommends a sixth shot on day 90.

The cost of post-exposure prophylaxis is not insignificant. In one US state, Massachusetts,

the cost was estimated to be between $2.4 million and $6.4 million for one year, 1995 [36]. The U.S. Department of Health and Human Services estimated that between 20,000 and 40,000 PEP treatments were given in the U.S. in the year 1997. Its suggested target goal for 2000 was 9,000 [37]. Although there are no published data to date whether this goal was reached, it seems unlikely. A recent CDC estimates suggest that in United States this treatment reaches approximately $300 million [38].

The public's reaction to recent cases of human rabies can be a difficult and demanding front of requests for rabies PEP, not always valid, from health care providers. After the first human rabies case in Israel in 25 years, there was a transient increase in persons requesting rabies PEP [39]. However, with firm adherence to the guidelines and the evanescent nature of the public reaction, health providers were able to supply rabies PEP per recommended guidelines [40]. Additionally, animal vaccinations were responsible, pari passu, for a decrease in the sylvatic red fox and golden jackal reservoirs and consequently, presumably, in the number of human exposures [41].

Conclusion

Rabies remains a major public health issue in many areas of the world. Recently, a novel and intensive treatment regimen was used to cure rabies in a non-vaccinated human being for the

first time in the known history of medicine. Before this, human rabies was one hundred percent fatal. The likelihood of reproducing this cure is unknown and, for the foreseeable future, rabies will continue to be a lethal disease. It is therefore essential to be aware of the local epidemiology of the disease, indications for and application of means of prevention and post-exposure prophylaxis.

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