Human rabies and its prevention

Rabies is an important health problem worldwide and is invariably lethal. As there is no cure, prevention is very important. This review provides a comprehensive report on prevention of rabies for health professionals from both developed and developing countries.

Rabies is one of the oldest diseases known to mankind and more than 40 000 people worldwide die from it each year in spite of the availability of newer cell culture vaccines. Louis Pasteur first immunized man against rabies with a vaccine nearly 120 years ago. According to the World Health Organization more than 2.5 billion people are still at risk of acquiring rabies (Haupt, 1999). Once the symptoms develop the mortality is almost 100%.

Although it is an animal disease mainly affecting dogs, it can be transmitted to humans by accident, most often through an animal bite. Rabies is common in China, south and south-east Asia and north America. Human rabies transmitted by bats has acquired greater epidemiological relevance in various Latin American countries. Several countries including UK, Iceland, Japan, Switzerland, Italy and Singapore are free from rabies.

Between 1946 and 2000, 21 people acquired the infection while abroad in rabies endemic areas and died in the UK because of it (Smith et al, 2003, 2005; Solomon et al, 2005). In 2001, two imported cases of rabies were reported – one was acquired in Nigeria and the other in the Philippines. In the UK, the last human death from indigenous rabies was recorded in 2002 (Smith et al, 2005). This death was caused by European bat lyssa virus type 2a acquired in Scotland. This does not affect the UK's status as rabies free as this applies to terrestrial mammals only.

Rabies is often not diagnosed until after death. A case report by Solomon et al (2005) indicated that a patient died of rabies in the UK which was acquired abroad. This emphasizes that doctors from rabies non-endemic areas should know about rabies and its management. This article provides an up-to-date summary on the pathogenesis, clinical features and prophylaxis of rabies and management of dog bites for both developed and developing countries.

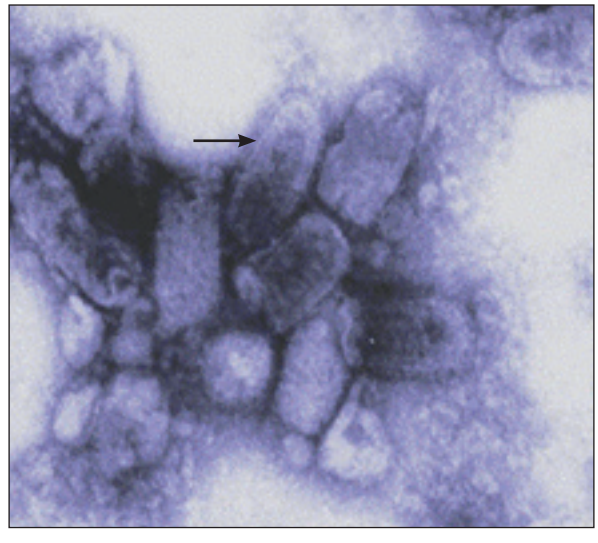
Rabies virus and its transmission

Rabies is caused by a RNA virus (*Figure 1*) of the rhabdoviridae family. It has a single strand of RNA, a phosphoprotein and a RNA polymerase which form a helical ribonucleoprotein complex. The rabies virus has a coat of glycoprotein(G) which determines the virulence (Warrell and Warrell, 2003). The virus is usually spread by the bite of an infected animal, but can also penetrate broken skin and mucosa, so being licked by an infected animal is also dangerous. Airborne infection from caves as well as in laboratories workers dealing with rabies virus has been well documented. The only documented evidence of human to human spread is via organ transplants. In 2004, four recipients of kidneys, a liver and an arterial segment from a common organ donor died of encephalitis of an unknown cause (Srinivasan et al, 2005). Investigations showed that three out of the four had antibody against rabies. Transplacental and infection via breast milk are extremely rare.

Pathogenesis

Rabies virus has a predilection for nerves, muscles and salivary glands. The virus spreads via peripheral nerves to the brain causing encephalomyelitis. Rabies causes widespread neuronal necrosis and inflammation, in particular it affects basal ganglia and midbrain. After the development of CNS infection, there is centrifugal spread of the rabies virus to extraneural (systemic) organs. Rabies virus antigen (RVA) is found in nerve plexuses of multiple organs, including the gastrointestinal tract. RVA is also observed in muscle fibres of the heart, tongue and larynx

Figure 1. Electron microscopy of negatively stained rabies virus (arrow).



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(Jackson et al, 2001). The adrenal medulla shows diffuse and intense mononuclear exudate associated with phaeochromocyte alterations in 60% of patients (Almeida Hde et al, 1986). There is no detectable immune response to rabies until the late stage, indicating that rabies somehow evades the immune system (Warrell and Warrell, 2003).

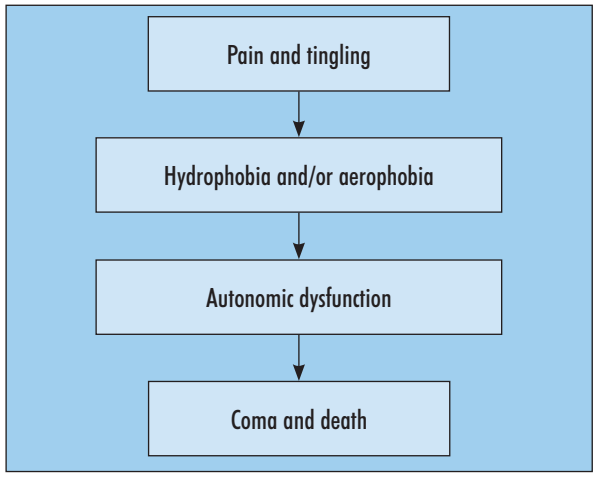
Microscopic examination of rabies-infected tissues often show eosinophilic intracytoplasmic inclusions, known as Negri bodies, containing masses of viral RNA, ribosomes and virions. In one study, Purkinje cells and periaqueductal gray neurons showed the largest percentage area of both Negri bodies and signal for RVA (Jackson et al, 2001). There may be a linear relation between RVA and Negri bodies. This means that those with more antigen should produce more Negri bodies although this is also influenced by the type of neuron.

Clinical feature

Rabies may mimic respiratory or abdominal infections or occasionally Guillain–Barré syndrome. There are two types of clinical presentations of rabies which are well known: encephalitic (furious) and paralytic (dumb) forms. Host immune responses may influence the clinical manifestations and course in human rabies.

In its encephalitic form (*Figure 2*), it can present with fever, insomnia, anorexia, headache, photophobia, agitation, dysarthria, visual hallucination, aerophobia, irritability and difficulty swallowing. Hydrophobia is a pathognomonic feature of rabies and is present in 95% of cases. It is a combination of inspiratory muscle spasm, with or without painful laryngopharyngeal spasm, associated with terror which is usually provoked by attempts to drink water (Warrell and Warrell, 2003). Involvement of the brainstem and hypothalamus may present with cranial nerve palsies, autonomic disturbances such as hypersalivation, lacrimation, hypotension, hypo- or hyperthermia or diabetes insipidus. Rabies causes an increase in CSF lymphocytes and a positive test for RVA. It can be differentiated from the cephalic form of tetanus as this has a shorter incubation period, the presence of trismus and normal CSF findings.

Figure 2. Typical course of rabies.



In the paralytic form, flaccid paralysis develops in the bitten limb which then ascends in symmetrical or asymmetrical manner. The patient ultimately develops paraplegia and dies of paralysis of the respiratory muscles. Hydrophobia is not common in this form. Other complications that may occur include adult respiratory distress syndrome, hypothermia, myocarditis and diabetes insipidus (Udwadia et al, 1989).

Diagnosing rabies

Antemortem

Diagnosing rabies once symptoms begin may not save the victim's life but will help to minimize exposure to others, allow for identification and prophylaxis of those who may have been exposed, and identify the animal vector. The suspected rabid animal should be killed and the brain tissue examined for Negri bodies by direct immunofluorescence which is a rapid, safe, sensitive and specific technique for diagnosing rabies.

In human, it may be difficult to diagnose rabies antemortem because of the non-specific presentation. The diagnosis may be confirmed by examination of a corneal impression, biological tests of the CSF and saliva, and visualization of Negri bodies in nervous tissue by direct immunofluorescence. Established diagnostic techniques, including the fluorescent antibody test (FAT), mouse inoculation test and the rabies tissue culture inoculation test, often fail to detect the virus, possibly as a result of insufficient viral load which can happen in early disease. Reverse transcription-polymerase chain reaction (RT-PCR) and sequencing will confirm the presence of rabies virus in both the saliva and skin specimens which can be easily taken from the nape of the neck (Smith et al, 2003). RVA may be demonstrable in the network of nerve fibres surrounding the hair follicles. Absence of virus in biopsies, saliva, serum and CSF may be caused by neutralizing antibodies, so a negative result for RVA does not exclude rabies.

Electroencephalograms do not show epileptiform activity. Both forms of human rabies share a similar magnetic resonance imaging pattern (Laothamatas et al, 2003). Non-enhancing, ill-defined, mild hyperintensity changes in the brainstem, hippocampi, hypothalami, deep and subcortical white matter, and deep and cortical gray matter can be demonstrated on T2-weighted images in the non-comatose patient with rabies.

Postmortem

At autopsy, rabies can be diagnosed by the presence of Negri bodies. Brain biopsy with a trucut needle inserted through the superior orbital fissure into the cranial cavity is an alternative to autopsy which may reduce the number of personnel who require post-exposure prophylaxis and avoids full necropsy if the deceased's relatives oppose this. However, Negri bodies are not present in all cases. Methods which are used to confirm rabies postmortem include Seller stain, FAT and intracerebral inoculation in newborn Swiss albino mice.

Treatment of established rabies

Established rabies is invariably fatal. The treatment includes maximum respiratory support, anticonvulsants, steroids, pressors, haemodialysis and interferon treatment. The patient should be treated in an isolated environment and the staff in contact should be immunized.

Prognosis

Rabies encephalitis remains essentially incurable. Most patients die at home, and their terrible symptoms are often unpalliated by sedatives or analgesics. There are six documented cases of recoveries from rabies.

Prevention of rabies

Table 1 summarizes the prevention of rabies. The individual aspects of prevention are discussed down below in detail.

Prophylaxis against rabies

Vaccines are used for active immunization against rabies while immunoglobulin provides rapid passive immunization. Both of them can be used together or simultaneously when the risk of developing rabies is very high. Prophylaxis is traditionally divided into pre-exposure and post-exposure prophylaxis.

How vaccination differs in rabies endemic and non-endemic areas

Most of the published literature on rabies is unclear about whom to vaccinate after a dog bite. In countries like India every dog bite is treated as though it was from a rabid animal, so every patient gets full vaccination ranging from human diploid cell vaccine (HDCV) to indigenous low cost vaccines. The only exemption is if the dog remains healthy for at least 2 weeks or if rabies is excluded from the dog's brain biopsy, but these are unusual. Indications for pre-exposure prophylaxis remain the same in both rabies endemic and non-endemic countries.

In the UK the 'green book' published by the Department of Health (2006) provides an overview on the prevention of rabies. When a patient is bitten by a dog, the health professional treating the patient should seek advice from the Health Protection Agency's virus reference department, the Communicable Disease Surveillance Centre or the Scottish Centre for Infection. The green book classifies patients into three risk categories (no risk, low risk and high risk) for post-exposure prophylaxis purposes. No-risk patients do not need vaccination against rabies, but those in the other two categories do. The risk assessment is based on the site and severity of the wound, the circumstances of the bite, and the appearance, vaccination status and origin of the animal. Specialist advisers from these centres will recommend appropriate vaccination and use of immunoglobulin. In the UK, the intradermal route is not advised for rabies vaccination. Intramuscular injection of the vaccines should be given in the upper arm or anterolateral thigh since fat in the gluteal region may interfere with absorption.

Table 1. Prevention of rabies

Eliminating stray animals
Immunization of pets
Oral immunization of selected wild animals
Pre-exposure immunization of persons at very high exposure risk
Rapid evaluation and treatment of humans following exposure
Six-month quarantine system for all cats and dogs entering the UK

Rabies vaccines

Although there are five anti-rabies vaccines available worldwide only two are commonly used in the UK: HDCV (Sanofi Pasteur, Berks, UK) and purified chick cell embryo vaccine (PCECV) (Rabipur, Novo Nordisk, Crawley, UK).

Human diploid cell rabies vaccine

HDCV is considered the gold standard for both pre- and post-exposure prophylaxis. A study showed that patients receiving HDCV plus antirabies hyperimmune gammaglobulin developed higher antibody titres (measured by enzyme-linked immunosorbent assay (ELISA) test) at the end of the vaccination schedule than those receiving the vaccine alone. Single-day immunization against rabies with HDCV vaccine has an unacceptably high failure rate.

The vaccine can be given intramuscularly or intradermally. In the UK, only the intramuscular vaccine is used while WHO recommended a intradermal regime. Some studies suggest that the intradermal route uses only 30% of the vaccine that is used in intramuscular route (Warrell et al, 1985) and produces an earlier antibody response. Intradermal HDCV was licensed for pre-exposure use in the United States in 1986 (Bernard et al, 1987). Although intradermal HDCV can be a cost-effective substitute for intramuscular vaccine, excessive use of unnecessary pre-exposure booster doses by any route may be inadvisable because of systemic allergic reactions.

Table 2 summarizes the side effects of HDCV. It can produce serum sickness-like hypersensitivity reaction.

Table 2. Side effects of human diploid cell vaccine

Pain at injection site
Erythema
Generalized itching
Regional adenopathy
Serum sickness-like hypersensitivity reaction
Wheezing

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The clinical reaction consists of delayed onset, generalized urticaria, and angioedema, with some arthralgias. Skin biopsy specimens demonstrated a leukocytoclastic vasculitis (Warrington et al, 1987). Immunoglobulins, especially IgE and IgG antibodies to beta-propiolactone and human serum albumin are associated with urticarial reactions to rabies vaccine. There is a new albumin-free HDCV (Lyssavac-HDC, Berna Biotech, Berne, Switzerland) which can avoid albumin-related side effects (Wilde et al, 1995). Simultaneous coincidental intake of chloroquine for malaria prophylaxis can reduce the antibody response to primary immunization with intradermal HDCV. A simple, sensitive, rapid method based on the principle of immunoadherence haemagglutination has been devised for the detection of rabies antibody (Budzko et al, 1983). A study showed that rabies neutralizing antibody titre ranged from 1:64 to 1:128 in the serum of patients when they were fully vaccinated (Madhusudana and Aggarwal, 1992).

Purified chick cell embryo vaccine

PCECV is cost-effective for rabies prophylaxis in developing countries. Several pre- and post-exposure controlled vaccine trials and clinical studies have shown that the PCECV, Rabipur, is as safe and effective as the rabies HDCV. PCECV does not result in immune-mediated hypersensitivity reactions following booster doses, unlike those seen in about 6% of patients receiving HDCV boosters following an initial series of HDCV (Dreesen, 1997).

Other vaccines and their complications

Duck embryo vaccine can cause anaphylaxis (Rosa, 1983). A 8-year-old boy died from rabies 20 days after a dog bite in spite of receiving nine injections of Semple's antirabies vaccine (Manghani et al, 1986). Chromatographically purified rabies vaccine administered intramuscularly to healthy adults is immunogenic and is associated with fewer local and systemic reactions than HDCV. It can cause headache, myalgia and malaise.

Rabies immune globulin

Rabies immune globulin (RIG) is essential for post-exposure prophylaxis (20 IU/kg body weight) but is expensive and not widely available (Hanlon et al, 2001). The importance of RIG in post-exposure rabies treatment is well known and local injection into the animal bite sites is crucial (Saesow et al, 2000). At present, preparations of purified human or equine RIG are used. However, neither of these reagents is readily available, entirely safe or consistent in their biological activity. An ideal reagent would consist of a panel of human monoclonal antibodies. Such antibodies are now available, their only drawback is the cost of production.

Pre-exposure prophylaxis

Pre-exposure prophylaxis is given to those who are likely to be exposed to rabies virus (*Table 3*). It involves three intramuscular doses of rabies vaccine, one each on days 0, 7 and 21 or 28, and further booster doses where required based on antibody titres. Studies suggest that HDCV may not always produce acceptable titres after intradermal pre-exposure prophylaxis (Fishbein et al, 1987). A study conducted by the National Institute of Virology, Pune, India, used only two doses of HDCV for primary pre-exposure prophylactic immunization; the interval between the two doses was approximately 4 weeks (Rodrigues et al, 1987). The majority of people who had been vaccinated retained detectable neutralizing antibody after pre-exposure prophylaxis for as long as 5 years and a single booster dose thereafter evoked a good antibody response. The immune status to rabies of 14 volunteers was determined using the commercially available Trousse Platelia Rage (Diagnostics Pasteur, Marnes la Coquette, France) ELISA test system (Oelofsen et al, 1991) and found that after the first booster, additional booster vaccinations at 5-yearly intervals would provide adequate prophylactic immunity.

Post-exposure prophylaxis

Modern human post-exposure prophylaxis consists of potent vaccines and local infiltration of RIGs, but the latter biologicals are not widely available or affordable. Monoclonal antibodies offer several advantages over RIGs. According to a recommendation from WHO (World Health Organization, 2006) for prevention of possible rabies infection, active vaccination has to be combined with application of immunoglobulin to get a fast protective effect. Humans exposed to rabies virus must be promptly treated by passive immunization with antirabies antibody and active immunization with rabies vaccine.

Unimmunized or incompletely immunized individuals

This includes those who have been immunized by the intradermal route, have received fewer than three doses of vaccine or whose last dose of vaccine was given more than 2 years previously. For patients in a low-risk area, a course of five or six injections is needed, given as one injection (1 ml) on days 0, 3, 7, 14, 30 and 90. The sixth

Table 3. Indication for pre-exposure prophylaxis

Veterinary surgeons
Animal handlers
Laboratory staff who handle the virus
Bat handlers
Health-care workers with risk of exposure to body fluids from a patient with probable or confirmed rabies

injection on day 90 is optional but is recommended by WHO for longer lasting seroprotection. Alternatively WHO recommend the abbreviated multisite schedule, the 2-1-1 regimen. It involves administration of one injection (1 ml) in the right arm and one injection (1 ml) in the left arm at day 0 and one injection (1 ml) into the deltoid muscle on days 7 and 21.

For exposure in a high-risk area a single dose of human RIG of 20 IU/kg of body weight is infiltrated as much as possible around the bite wound. Any remaining solution is administered by intramuscular injection. At the same time the first dose of either of the vaccination schedules suggested for exposure in a low-risk area is administered. Continue vaccination until the course is complete. The recommended dose of human RIG should not be increased or repeated as it may interfere with antibody formation during rabies vaccination.

Immunocompromised patients at high risk of contracting rabies should be given the vaccination schedule of five or six injections. Additionally the first dose should be doubled and administered as a single dose injected into the right and a single dose injected into the left deltoid muscle as soon as possible after exposure. It is recommended that the levels of antibody should be determined 3–4 days after the third dose of vaccine. If the rabies antibody levels are below the value considered sufficient to provide protection (0.5 IU/ml) a double dose of vaccine should be given immediately.

Fully immunized individuals

One injection of vaccine (1 ml) on days 0 and 3 is all that is required. Administration of human RIG is not essential. It is not necessary to maintain intervals between rabies vaccine and other vaccines.

Pet vaccination

Although pet vaccination and stray animal control remain the cornerstones of human rabies prevention, the risk of rabies by the non-bite route (e.g. raccoon saliva on pet dogs' and cats' fur) should also be considered (Wyatt et al, 1999). Under the Pet Travel Scheme (Department for Environment, Food and Rural Affairs, 2006) pet animals from certain countries to are allowed to enter the UK without quarantine as long as they meet the rules. So people in the UK can take their pets to other European Union (EU) and certain non-EU countries, and return with them to the UK without the need for quarantine (McKay and Wallis, 2005).

KEY POINTS

- Hydrophobia is pathgnomonic of rabies.
- Prevention with antirabies vaccine is vital.
- Dog bites also require vaccination against tetanus.
- Primary suturing of dog bites should be avoided if possible.

HIV and vaccination

Human immunodeficiency virus (HIV)-infected patients with low CD4(+) T lymphocyte counts have shown a poor neutralizing antibody response to pre- and post exposure rabies vaccination (Tantawichien et al, 2001).

Managing dog bite

Management of dog bites is outlined in *Table 4*. In the UK specialist advice should always be sought for both post-exposure prophylaxis and management of rabies. Immediate closure of the wound is avoided except on the face which should be repaired under antibiotic cover with general anaesthesia to avoid facial scarring.

Conclusions

Rabies is a highly lethal infection. Clinical suspicion is very important in diagnosing rabies because of its non-specific presentation. RT-PCR of saliva, skin and other bodily fluids may help to confirm the diagnosis. Autopsy of suspected animals will show Negri bodies in the brain. Dog bites should treated with debridement and avoidance of primary closure except on the face where primary closure is advisable to prevent cosmetic problems. Since there is no cure for this condition, elimination of stray dogs and immunization of those at risk remain the main strategies in controlling rabies. BJHM

Figure 1 *is reproduced courtesy of the Wadsworth Centre, New York State Department of Health, USA.*

Conflict of interest: none.

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Table 4. Treatment of dog bite

Cleanse area with soap and water
Treat with alcohol (70%), povidone iodine or 1.1% solution of quaternary ammonium compound.
Bite injuries should not be closed with a suture or only sutured to secure apposition
Give prophylaxis against tetanus
In the UK seek advice from the Health Protection Agency
In rabies endemic areas follow local protocol. If there is no protocol vaccinate based on previous immunization
Give antibiotics to protect against bacterial infection

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