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Rabies

NOTIFIABLE

Introduction

Rabies is an acute progressive viral infection, which, if left untreated leads to an almost invariably fatal encephalomyelitis, death resulting from respiratory paralysis. Members of the lyssavirus genus cause rabies. Rabies has traditionally been associated with the Genotype 1 form (classical or sylvatic rabies); another six genotypes are known to produce disease.

In recent years, rabies has become recognised as an emerging zoonosis originating in bats; rabies-related bat lyssaviruses implicated in human disease include European Bat Lyssaviruses (EBLV) and Australian Bat Lyssavirus (ABLV). These variants present in humans in ways that are clinically indistinguishable from classical rabies.

Epidemiology

The WHO records between 40,000 and 70,000 cases of human rabies annually, most in less-developed countries. All continents except Antarctica report animal cases, although individual countries are reported to be rabies-free. Any warm-blooded animal may be infected but amongst domestic animals, dogs and cats are most commonly infected. Globally, over 90% of all human infections result from dog bites. The main source of human rabies in developing countries is from stray or feral dogs and cats and in developed countries the risk arises mainly from wild animal sources. In endemic areas, children are at particular risk.

In the United States, amongst wild animals, skunks, racoons and bats

account for 85% of animal cases of classical rabies; the incidence has been rising there since the 1950s. In Latin America, vampire bats carry classical rabies. Elsewhere, monkey bites have been known to transmit the virus. The development of international travel, and the capacity for greater numbers of people to travel to more exotic and remote locations, puts many more people at risk now than was the case in the past.

It should be emphasised that any bite, lick or scratch from any warm-blooded animal in an endemic area must be considered as a high risk and further specialised advice should be sought as soon as possible. In Europe, foxes have been the primary host but there has been extensive infection among dogs and cats. Vaccination of foxes (and certain domestic species) has led to the dramatic decline in vulpine rabies in Western Europe in the last 20 years, although foxes remain a significant source of rabies in Eastern Europe and Turkey.

Certain countries that are declared rabies-free have rabies-related viruses (bat lyssaviruses) in their bat populations, e.g. Australia and the UK. In the UK, rabies-related viruses have only been detected in Daubenton's bats but not in the commonest UK bat species, the Pipistrelle.

The issue of EBLV has become a concern recently; an ongoing survey in the UK has demonstrated that four bats have been identified as having been infected with EBLV. In addition, in 2002 an unvaccinated bat handler in Dundee in Scotland died of EBLV, having been bitten by a bat. Only 3 other cases of EBLV infection (all fatal) have been reported in the past 30 years in Europe. In order to assess the risk of EBLV in Ireland, the Department of Agriculture and Food is undertaking a survey of Daubenton's bats for EBLV. This survey was initiated in 2002 and is ongoing.

Transmission

Infection is usually transmitted by the bite (or scratch) of a rabid animal. The virus may also be passed when infected saliva comes in contact with broken or grazed skin, with mucous membranes and with the cornea. In addition, laboratory workers manipulating the virus or clinical specimens containing the virus are at potential risk of occupational contact or inoculation. Aerosol transmission is considered possible (possibly accounting for certain lab-acquired cases; this method may also be important in rabies-infected bat caverns). Human-to-human transmission is rare and the only documented cases involve corneal and solid organ transplantation.

Effects of rabies

The incubation period of rabies is generally between 2 and 12 weeks but may range from 9 days to 2 years or even longer. The wide variation in incubation is thought to depend, in part, on the site of inoculation, the severity of the wound, and the amount of virus introduced. The factors that tend to reduce the incubation period include inoculation occurring closer to well-innervated parts of the body (including primary nerve bundles and the brain) and deeper and more extensive wounds (which will tend to allow an increased viral load into the wound). The duration tends to be shorter in children than adults.

Rabies has the highest case-fatality ratio of any infectious disease. Untreated, symptomatic disease is almost invariably fatal; the majority of the half dozen or so documented cases of survival from rabies had had some form of pre- or post-exposure treatment.

Initial virus replication takes place in the tissues at the point of entry, persisting for between 48 and 72 hours. It progresses along the axonal sheaths in peripheral nerves towards the central nervous system. Viral spread then occurs to the peripheral nerves, largely out of reach of circulating antibody; there is no antibody response until the onset of clinical symptoms.

The symptoms of rabies are highly variable. Early symptoms are non-specific and include pain and paraesthesiae at the inoculation site. Low-grade fever, malaise, anorexia, headache, nausea and vomiting and even sore throat are all commonly reported. Depending on the parts of the CNS affected, the patient may be excitable, irritable with more classical hypoglossal spasm associated with water (hydrophobia) or blowing in the face (aerophobia) or more obtunded with an ascending paralysis. Rising intracranial pressure leads to the decreased level of consciousness and the development of focal convulsions. Central and peripheral nervous impairment will lead to progressive respiratory distress. A wide variety of cardiac dysrhythmias can occur.

Other causes of viral encephalitis, Guillain-Barré syndrome, tetanus, poliomyelitis and the toxic effects of drugs and poisons are among the differential diagnoses.

A. PRE-EXPOSURE PROPHYLAXIS

Rabies vaccines

Rabies vaccine is used for pre-exposure protection of those at risk. One type of rabies vaccine, human diploid cell rabies vaccine (HDCV), is a

freeze-dried suspension of Wistar rabies virus strain PM/W1 38 1503-3M cultured on human diploid cells and inactivated by beta-propiolactone. The potency of the reconstituted vaccine is not less than 2.5 IU per 1 ml dose. The freeze-dried vaccine should be stored at 2-8°C. It should be used immediately after reconstitution with the diluent supplied and any unused vaccine discarded after 1 hour. It may be given by intramuscular injection, usually in the deltoid region or anterolateral region of the thigh (never in the buttocks). The manufacturer's recommendations should be consulted prior to administration. The vaccine contains traces of neomycin and human albumin.

An alternative vaccine that may be used is purified chick embryo cell vaccine. This contains inactivated rabies virus (Flury LEP). The potency of 1 ml is greater than or equal to 2.5 IU. The vaccine should be kept refrigerated. The recommended dose is 1 ml intramuscularly. The vaccine should be given in the deltoid or antero-lateral part of the thigh. Intra gluteal injection is not recommended. Patients with a history of severe hypersensitivity to eggs or egg products should not receive this vaccine for pre-exposure prophylaxis. This vaccine may also contain trace residues of polygeline, amphotericin B, chlorotetracycline or neomycin.

Ideally a pre-exposure course should be completed using one type of cell culture vaccine throughout the primary course, but if one type of cell culture vaccine is unavailable then another may be substituted.

Indications

Pre-exposure prophylaxis should be offered to those in the following categories:

- Laboratory workers handling or potentially handling the virus
- Those, who by the nature of their work are likely to be in direct contact with imported animals:
 - Staff at animal quarantine centres
 - Staff at zoos
 - Staff at research and acclimatisation centres where primates and other imported animals are housed
 - 'At-risk' staff at sea and airports, e.g. Dept of Agriculture and Food Inspection Staff
 - Authorised carrying agents for imported animals
- Selected National Parks and Wildlife Staff who may handle bats, based on risk assessment
- Dog wardens and other relevant staff in the Local Authorities
- Workers in enzootic areas abroad at special risk (e.g. veterinary staff, zoologists)
- People who regularly handle bats

- Health-care workers who have, or are about to, come into close contact with a patient (or their clinical specimens) with probable or confirmed rabies
- Those living or travelling in endemic areas who may be exposed to the risk of being infected or are undertaking journeys in remote parts where medical treatment may not be immediately available
- Staying in highly endemic areas for more than 4 weeks (particularly in the case of children).

Dose and route of administration

For primary pre-exposure protection, three 1.0 ml doses of HDCV should be given, one each on days 0, 7, 21 **OR** 28 by intramuscular injection in the deltoid region or anterolateral region of the thigh. The same dose is used for adults and children. All travellers to areas of risk should be informed by their medical advisors to seek immediate medical aid if an animal bite or scratch is sustained. They should be given advice on wound toilet – see *Standard Operating Procedure for Risk Assessment and Management of Non-Indigenous Rabies Exposure* available at www.hpsc.ie.

Contraindications

Anaphylactic reaction to a preceding dose or any of the constituents.

Precautions

Pre-exposure vaccine should only be given to pregnant women if the risk of exposure to rabies is high.

Adverse reactions

Local: HDCV may cause local reactions such as redness, swelling or pain at the site of injection within 24-48 hours of administration.

General: Systemic reactions such as headaches, fever, muscle aches, vomiting and urticarial rashes have been reported. Anaphylactic shock has been reported from the USA and Guillain-Barré Syndrome from Norway, although no causal relationship between Guillain-Barré syndrome and rabies vaccine has been established. Reactions to the vaccine may become more severe with repeated doses.

The initial primary dose pre-exposure course produces protective antibody in virtually 100% of recipients and makes routine post-immunisation serological testing unnecessary.

Rabies vaccine will induce long-lasting memory giving rise to an accelerated immune response when a booster dose of vaccine is administered.

- Periodic booster injections are therefore not recommended for general travellers.
- In the event of a significant animal exposure, persons who have previously been immunised should receive 2 further doses of rabies vaccine.

B. CONTINUED OCCUPATIONAL EXPOSURE

The following groups are managed as outlined below:

For those people who have continuous occupational exposure and where exposure is likely to go unnoticed, e.g. rabies research laboratory workers and rabies vaccine production workers, serological testing should be carried out at 6-monthly intervals and boosters administered when the antibody level goes below a predetermined level – less than 0.5 IU/ml.

For those who have frequent episodic exposure, e.g. rabies diagnostic workers, veterinary surgeons and staff, wildlife rangers who are conducting bat research, serology should be carried out every 2 years and boosters administered as necessary.

For those who are at greater risk than the population but have only potential episodic exposure and can report exposures, e.g. dog bites. In the absence of an exposure, these staff do not require further booster doses/ serological testing once primary immunisation has been completed.

The current best advice is that boosters should not be administered more frequently than every 2-3 years to minimise the possibility of localised reactions to the vaccine.

Serological testing is otherwise only advised for those who have had a severe reaction to a previous dose of vaccine to determine the necessity of a booster dose.

Further information on rabies vaccine and post-exposure treatment is available from the Irish Medicines Board, Cherry Orchard Hospital, Health Protection Surveillance Centre and from the Health Service Executive.

C. POST-EXPOSURE TREATMENT

Travellers who have been exposed to the possibility of rabies while abroad should seek immediate medical attention. On return to Ireland they should contact their General Practitioner or specialised vaccination centre or infectious diseases department to receive further advice. Similarly, anyone having received a bat bite in Ireland or the UK should seek immediate medical attention.

Treatment, including wound toilet, must not be delayed, and should be started as soon as possible while enquiries are made about the local epidemiology of rabies in the country concerned (see above) and, where possible, the ownership and condition of the biting animal and the vaccination status of the animal should be determined.

The immediate steps to be taken are as follows:

- 1 **Wound toilet:** As soon as possible after the incident, the wound or site of exposure (e.g. mucous membrane) should be thoroughly cleaned with water under a running tap for at least 10 minutes. The wound should be **initially** washed thoroughly (with soap or detergent and water) and then rinsed completely. It is important not to mix disinfectant with soap during washing, as detergents can negate the effects of disinfectant. A suitable disinfectant (e.g. povidone-iodine solution or 70% alcohol) should be applied and the wound covered with a simple dressing. Tetanus prophylaxis and measures to control bacterial infection should also be administered as indicated. Suturing should be delayed where at all possible (taking into account cosmetic factors and the potential for bacterial infections).
- 2 **Risk assessment:** Each case of possible exposure requires a careful and thorough risk assessment along the lines laid out below:
 - **Country of exposure (or the country of origin of the animal):** Depending on the country of exposure, the patient will be considered to be at 'No Risk', 'Low Risk' or 'High Risk'. (Up-to-date information on rabies by country can be found in World Health Organization, Rabies Bulletin Europe: www.who-rabies-bulletin.org/ or Centre for Disease Control and Prevention, USA: www.cdc.gov/ncidod/dvrd/rabies/epidemiology/epidemiology.htm).
 - **The type, severity and site of the wound:** Highest risk wounds involve piercing and breaking of the skin or involvement of mucous membranes.
 - **Circumstances of bite:** Unprovoked bites are more worrying and carry a much higher risk than provoked bites.

- **The species, behaviour and appearance of the animal:** Crazy or frantic animals pose a very significant risk. Bat rabies may be suspected if the bat is sick, grounded without injury or if an uninjured bat is found dead. Apparently healthy bats may have rabies. That said the risk of bat rabies in Ireland is likely to be very small. Table 20.1 shows the assessment of post exposure treatment requirements from significant bat bites sustained in Ireland and UK.
- **Vaccination status of the animal (if known):** Regularly vaccinated animals are much less likely to have rabies.
- **Immune status of the individual involved:** Fatal rabies encephalomyelitis is extremely unlikely in a fully immunised individual and is virtually certain to be prevented by an effective course of post-exposure treatment, if given sufficiently early.

Table 20.1 Assessment of post-exposure treatment requirements from significant bat bites (Ireland and UK)

Rabies risk	Unimmunised /incompletely immunised individual ¹	Fully immunised individual
Insignificant Contact, but no lesions; indirect contact; No contact.	None	None
Minor significance Licks of the skin; Scratches or abrasions; Minor bites (covered areas of arms, trunk, and legs)	Five doses (each 1.0 ml) rabies vaccine on days 0, 3, 7, 14 and 30	Two doses (each 1.0 ml) rabies vaccine on day 0 and day 3
Major significance Licks of mucosa; Major bites (multiple or on face, head, finger or neck)	Five doses (each 1.0 ml) rabies vaccine on days 0, 3, 7, 14 and 30, plus HRIG on day 0 only	Two doses (each 1.0 ml) rabies vaccine on day 0 and day 3

¹Persons who have not received a full course of pre- or post-exposure tissue-culture rabies vaccine

- 3 Post-exposure immunisation and immunoglobulin.** Specialist advice should be sought when post-exposure immunisation and immunoglobulin seems indicated. All immunosuppressed subjects

should be given HRIG following exposure. Table 20.2 provides guidance on the administration of HDCV and HRIG depending on the level of risk as dictated by the country of exposure.

Table 20.2 Post-exposure treatment requirement by country of exposure (for overseas exposure or by exposure to overseas animal)

Rabies risk	Unimmunised /incompletely immunised individual ¹	Fully immunised individual
No risk	None	None
Low risk	Five doses (each 1.0 ml) rabies vaccine on days 0, 3, 7, 14 and 30	Two doses (each 1.0 ml) rabies vaccine on day 0 and day 3
High risk	Five doses (each 1.0 ml) rabies vaccine on days 0, 3, 7, 14 and 30, plus HRIG on day 0 only	Two doses (each 1.0 ml) rabies vaccine on day 0 and day 3

¹Persons who have not received a full course of pre- or post-exposure tissue-culture rabies vaccine

Rabies-specific immunoglobulin

Human rabies immunoglobulin (HRIG) is obtained from the plasma of immunised human donors. It is used after exposure to rabies to give rapid protection until rabies vaccine, which should be given at the same time, becomes effective. After thorough wound cleansing, HRIG should be infiltrated into the depth of the wound and around the wound as much as anatomically feasible. Any remainder should be injected at an intramuscular site distant from that of the vaccine inoculation, e.g. anterior thigh (not gluteal region). The dosage is calculated based on body weight (20 IU/kg body weight).

Adverse reactions

HRIG may cause local reactions and low-grade fever but no serious adverse reactions have been reported.

Vaccine and HRIG suppliers

Post-exposure prophylaxis with the HDCV is currently available free of charge through the National Fever Hospital in Cherry Orchard. A supply of Human Rabies Immunoglobulin (HRIG) will also be maintained at this centre. Contact Dr. O'Dea, Tel. (01) 620 6000

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HRIG is also available from CDSC HPA, 61 Colindale Avenue, London NW9 5EQ, Tel. (00 44) 181 2006868.

It is essential that post-exposure treatment is started as soon as possible after exposure. Moreover, treatment should be considered, irrespective of the period between exposure and presentation unless the individual is previously vaccinated and rabies antibodies can be detected. The decision to administer HRIG should be based on a risk assessment and specialist advice should be sought.

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