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Rabies is a lethal infection that is prevalent in many regions worldwide. It can be prevented by vaccination and by prompt post-exposure treatment

Rabies: risk, prognosis and prevention

In this article...

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Abstract Driver C (2014) Rabies: risk, prognosis and prevention. *Nursing Times;* 110: 14, 16-18.
While the UK was declared free from rabies over 100 years ago, the disease remains a significant cause of death in many other countries around the world. It is hoped that eradication programmes in affected countries will succeed in the long term but, until then, prompt and thorough treatment can prevent people who have potentially been in contact with the rabies virus from developing this infection. This article provides a review of the disease and its prevention.

Rabies has the highest case-fatality rate of any known infectious disease. The disease is present in every continent of the world except Antarctica, and is endemic in more than 100 countries. It is estimated that each year up to 55,000 people (150 per day) die from this lethal but preventable infection (World Health Organization, 2010).

Increasing numbers of people from the UK are choosing to travel to countries where rabies is hyperendemic and, during the last eight years, three British women have died of this disease through quite innocuous bites from young animals (Public Health England, 2013). All three women failed to take the necessary action after their encounters with these animals, which highlights the importance of rabies awareness among all health professionals in the UK – even if they do not commonly advise those travelling abroad. A chance conversation with a patient, family member or friend may reveal potential exposure or intention to travel abroad, which offers an opportunity to explain the importance of pre-travel health advice and to dispel some of the myths associated with rabies.

Rabies infection

Rabies is an acute viral infection that causes progressive and usually fatal encephalomyelitis that is zoonotic (transferred from animals to humans). The WHO suggests that, without post-exposure prophylaxis, the global annual death toll would be as high as 327,000. The majority of cases occur in children under 15 years, although any age group is susceptible. While any mammal could carry the disease, 99% of human cases result from encounters with dogs (WHO, 2010).

Rabies virus (RABV) belongs to a group of viruses called lyssaviruses (from the Greek *lyssa* meaning rage), 11 of which have been identified. RABV is associated with canine rabies but all lyssaviruses are highly neurotropic and can cause acute progressive encephalomyelitis in humans. Bats worldwide have been found to be reservoirs for lyssaviruses.

Infection usually occurs following a bite or scratch that breaks the skin, but is also possible if infected saliva has contact with the mucosa or fresh open wounds. In rare cases, it has also resulted from inhalation of infected secretions, for example in a bat-infested cave (WHO, 2010). The virus replicates in non-nervous tissues then enters peripheral nerves and travels towards the brain.

The incubation period is generally the range of 20-90 days but can be as short as a few days or longer than a year (Jackson,

5 key points

1. Rabies is a lethal infection that cannot be cured
2. It is present in every continent of the world (except Antarctica) and kills at least 55,000 people every year
3. All health professionals in the UK should be aware of rabies even if they do not commonly advise overseas travellers
4. Prevention includes pre-exposure vaccination and post-exposure vaccine
5. The type of post-exposure prophylaxis required is dependent upon the individual's vaccination status

2007). Shorter incubation periods may be associated with wounds in highly innervated parts of the body such as the head, neck or hand, where the virus may enter nerves rapidly.

After infecting the brain, the virus replicates and spreads via nerve pathways to other organs including the salivary glands. Since it is concealed from the immune system during its initial activity in the nervous system, antibodies cannot be detected until the second week of symptomatic illness, so there is no test available to check for rabies infection before symptoms develop (WHO, 2010).

Clinical rabies is a continuum, not a series of easily defined stages (WHO, 2010). Once the virus reaches the central nervous system, it may cause one of two distinct forms of disease:

- Classical or encephalitic (furious) rabies, affecting 70% of infected patients;
- Paralytic (dumb) rabies, affecting 30% of infected patients.

Classical rabies

Clinical illness begins with malaise, anorexia, fatigue, headache and fever. Pain or paresthesia at or near the site of exposure is reported in 50-80% of cases (Rupprecht and Plotkin, 2013), while vague apprehension, anxiety, agitation, irritability, nervousness, insomnia or depression may be prominent during this period. Encephalitic disease progresses after this prodromal period of 2-10 days. Box 1 lists signs of nervous system involvement, which are seen alongside febrile illness.

Periods of hyperactivity lasting 1-5 minutes may occur spontaneously or be precipitated by a variety of tactile, auditory, visual or other stimuli; between these periods, patients are usually cooperative and able to communicate. Most patients develop hydrophobia and aerophobia.

Attempts to drink or eat may produce severe painful spasms of the pharynx and larynx and precipitate episodes of hyperactivity. Subsequently, simply the sight of liquids or stimuli of running water may cause pharyngeal spasms. Bright lights, loud noises, and air currents may also precipitate spasms.

Intensive medical care can offer cardiovascular and respiratory support and sedation to reduce patient distress; death is generally due to paralysis of the cardiorespiratory system, which occurs around five days after onset of symptoms (Rupprecht and Plotkin, 2013).

BOX 1. **SIGNS OF NERVOUS SYSTEM INVOLVEMENT**

- Hyperactivity
- Disorientation
- Hallucinations
- Seizures
- Bizarre behaviour
- Meningism
- Paralysis

Dog with suspected rabies: 99% of human cases result from encounters with dogs

Paralytic rabies

The paralytic form of rabies can be difficult to diagnose and may be confused with Guillain-Barré syndrome. Flaccid muscle weakness develops early in disease and may be associated with sphincter involvement, myoedema (localised contraction of muscles if tapped with a tendon hammer) and phobic spasm, including hydrophobia. Patients with paralytic rabies may survive for almost two weeks, with death resulting from respiratory paralysis (Dacheux et al, 2011).

Treatment

There have only been a handful of survivors of rabies, the most recent in 2004. Unfortunately, the efficacy of the treatment used on this patient, known as the Milwaukee protocol, was not subsequently confirmed, as all published attempts to reproduce the effect have been unsuccessful (Dacheux et al, 2011).

Work to identify an effective antiviral treatment against human rabies continues. In the meantime, the essence of medical care for these patients is isolation in a peaceful environment and supportive palliative care.

Prevention

There is no cure for symptomatic disease and no test for rabies infection before the onset of symptoms, so all travellers to endemic areas should be advised to avoid contact with animals – especially dogs – and should seek urgent post-exposure prophylaxis if they are put at risk.

There is no conclusive sign of infection in animals, and even pets that are apparently vaccinated should be regarded as a potential risk. Doctors in developing countries may be unaware of the correct treatment protocol so it is vital that travellers know about post-exposure management. They should also be aware that they may have to travel long distances to receive the correct treatment.

There are two approaches to prevention of rabies in humans:

- Pre-exposure vaccination followed by a reduced post-exposure vaccine (PEP) schedule;
- Rabies immunoglobulin accompanied by PEP.

Rabies immunoglobulin is not readily available everywhere in the world and travellers need to understand the risks of rabies exposure and how to deal with a situation should it arise.

Rabies vaccine

Louis Pasteur and his colleagues developed the first rabies vaccines, which were used for post-exposure treatment in 1885. These crude vaccines were manufactured from the nerve tissue of infected rabbits and administered daily for up to 21 days depending on the site of the bite. Victims of dog bites from across the world were sent to Paris to receive this treatment, including 20-170 British patients a year from 1885 to 1900 (Pemberton and Warboys, 2007).

In 1911 David Semple, a British Army physician working in India, developed an inactivated vaccine using infected sheep brains (Baer, 2007); this was delivered by a series of extremely painful injections into the stomach administered over 7-14 days. The World Health Organization (2010) has called for a ban on the production of this vaccine due to significant side-effects and because safer and more effective vaccines are now available.

Modern cell-cultured vaccines (CCV), pioneered in the 1950s, are now widely available; these have an excellent safety and efficacy record but their cost can be

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too high for poorer communities. CCVs are usually available through private healthcare providers and the International Society for Travel Medicine has a worldwide directory of clinics stocking these vaccines (available to members at www.istm.org). These inactivated vaccines are administered in the deltoid muscle in the same way as most other modern vaccines.

Studies have shown long-lasting immune memory in those who have received a three-dose series of CCV, and travellers do not need routine boosters (Salisbury and Ramsey, 2013; WHO, 2010). Expert advice should be sought for those who are immunocompromised.

People whose occupation puts them at continual or frequent risk of exposure (such as laboratory technicians, bat handlers and those working in quarantine centres) should receive a single reinforcing dose 12 months after the primary series of vaccinations. Periodic boosters may be necessary but antibody levels should be checked if possible and vaccination offered only if titres drop below 0.5IU/mL; health professionals should check the guidance on exact timing of these checks as national guidelines vary.

Contraindications

Patients with history of anaphylaxis to a previous dose or any constituent of the vaccine should not be given pre-exposure vaccination, while pregnant women and children aged under one year should only be given it after thorough risk assessment and expert advice.

In view of the almost certain fatality of rabies infection, there are no contraindications to post-exposure vaccination. If the patient history suggests an increased risk of anaphylaxis, vaccination should be given in a situation where this can be adequately monitored and treated (Salisbury and Ramsey, 2013).

Intradermal administration

Although there is robust evidence that rabies vaccine is equally effective if administered via the intradermal route, it is only licenced for intramuscular administration in the UK. In addition, health professionals require training and practice in intradermal injection, as incorrect administration may render the vaccine ineffective. Prescribers must take full responsibility for off-label administration (Salisbury and Ramsey, 2013).

Rabies immunoglobulin

There are three types of rabies-specific immunoglobulin: human rabies immunoglobulin (HRIG), equine rabies immunoglobulin (ERIG), and F(ab´)2 – a highly purified product derived from ERIG.

HRIG is the most efficacious and associated with the fewest adverse reactions; it is the preferred product, especially where there are multiple wounds around the head, face or hands but is extremely expensive and in short supply, especially in resource-poor countries. Modern ERIG is much cheaper and is now highly purified so adverse events have been reduced, so it should be used if HRIG is unavailable. However, anaphylaxis still occurs at a rate of 1/45,000, so ERIG should only be administered where there are facilities for dealing with anaphylaxis (WHO, 2010).

Post-exposure treatment

Immediate first aid

Wounds should be washed immediately with soap and running water for about 15 minutes then treated with antiseptic, preferably iodine based. Suturing should be delayed until after post-exposure prophylaxis has started (WHO, 2010).

Post-exposure prophylaxis for unvaccinated people

Rabies-specific immunoglobulin (RIG) is infiltrated around the wound or wounds, offering some immediate protection while the patient's immune system responds to active vaccination. For multiple bites, RIG may need to be diluted so that all wounds can be infiltrated. If a wound site is too small to receive the complete RIG dose (for example, if it is on a finger) as much as possible should be injected into the wound and the remainder injected into a large muscle distant from the site of administration of the first dose of vaccine.

- A five-dose course of CCV should be administered intramuscularly on days 0, 3, 7, 14 and 28;
- If CCV has been given in the absence of RIG and more than seven days have elapsed, it is considered unnecessary to administer RIG;
- As the incubation period is unpredictable, anyone presenting with a history of a potential exposure should be assessed for PEP, no matter how long since exposure. National guidelines should be checked for contact details for expert opinion; in the UK, this information can be found on the websites of Public Health England (tinyurl.com/PHE-rabies) and Health Protection Scotland (tinyurl.com/HPS-rabies) website, and in *The Green Book* (Salisbury and Ramsey, 2013).

Pre-exposure vaccination

Pre-exposure vaccination consists of three doses administered intramuscularly on days 0, 7 and 21-28. Intervals should not be reduced but longer intervals will not impair the immune response.

It is generally considered unnecessary to restart a course of vaccines in an immunocompetent individual even if a significant time has elapsed since the previous dose. Travellers should be advised to take their vaccine records with them, as documentary evidence is essential in any assessment for post-exposure treatment.

Post-exposure prophylaxis for vaccinated people

Patients who have received three doses of vaccine in the past do not require RIG. Immediate first aid measures are still important and two doses of vaccine should be given as soon as possible on days 0 and 3. These doses boost existing immune memory, ensuring sufficient circulating rabies antibodies.

Patients who have received fewer than three doses of pre-exposure vaccine should be advised to try to obtain full PEP including RIG (WHO, 2010).

Conclusion

Rabies is a lethal infection that can be prevented by prompt, correctly administered post-exposure treatment.

All those who travel to rabies-endemic regions need to be aware of the risks and how to deal with a potentially rabies prone incident. The Global Alliance for Rabies Control is working to eradicate the disease – further information can be found at rabiesalliance.org **NT**

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