Review Article

Pediatric Education and Research
Volume 1 Number 3, July - September 2013

Rabies- A Public Health Perspective: An Update

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Abstract

Rabies is severe encephalitis transmitted to humans by the bite of a rabid animal, usually a dog or various wild mammals that form natural reservoirs. Exposure to certain species of bats, even without a known bite, can also lead to rabies. Rabies is a fatal viral disease transmitted from animals to humans. It causes more than 35,000 human deaths per year. Among the diseases of viral origin, rabies is unique in its distribution and range of victims since it can afflict all warm-blooded animals. Children are particularly susceptible to get rabies as of their small stature and they have no fear of animals, so they are bitten easily. The interaction between the virus and the host population has facilitated the survival of the disease. The rabies virus (RV) has not changed in any significant way and has been capable of taking advantage of conditions suited to the continuance of rabies. Infection by RV is invariably lethal in the absence of protective immune response which, however, can contribute to the pathogenesis of rabies. Pro-inflammatory cytokines might affect, directly or indirectly, the levels of neurotrophins, growth factors, neurotransmitters and neurotoxins in the brain by activating glia, neurons, and vascular and immune cells.

Keywords: Rabies; Vaccine; Post exposure prophylaxis.

Introduction

Rabies is one of the most feared diseases in human history, with reports of recognizable cases dating back to the 23rd century BC. Rabies is a zoonosis that can affect both wild and domesticated animals. Although many mammals may become infected, the prevalence of infection varies considerably from continent to continent. Increasingly, bats have been recognized as an important reservoir. Transmission in humans occurs primarily through the bite of an infected animal; in the United States, it most commonly comes from bats.[1-5] Human-to-human transmission of rabies has been described. There have been 8 documented cases of rabies transmission through corneal transplants, of which 1 occurred in the United States.[6-7] Rabies affects all age groups, but is most common in children younger than 15 years of age. Children are at higher risk of rabies exposures due to their smaller stature and lack of fear towards animals. Approximately 40% of post-exposure immunizations are administered to children between 5 and 14 years of age.[8,9]

There have been no previously reported cases of rabies transmission through solid organ transplantation.

Etiology

Lyssavirus is one of the seven genera that form the family Rhabdoviridae, within the

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(Received on 23.08.2013, Accepted on 09.09.2013)

order Mononegavirale. It comprises classical rabies virus (RABV; genotype 1), Lagos bat virus (LBV; genotype 2), Mokola virus (MKV; genotype 3), Duvenhage virus (DV; genotype 4), European bat lyssavirus 1 (EBLV-1; genotype 5), European bat lyssavirus 2 (EBLV-2; genotype 6), and Australian bat lyssavirus (ABLV; genotype 7). Recently, four additional viruses, isolated from insectivorous bats, have been proposed as new members of Lyssavirus genus: Aravan virus (AV), Khujand virus (KV), Irkut virus (IV), and West Caucasian bat virus (WCBV).[10-13]

Rabies viruses are bullet-shaped structures of about 75 nm X 200 nm and can be roughly divided into a structural and a functional unit: the viral envelope and the ribonucleocapside core. Five monocistronic genes relate to five viral proteins: The N gene codes for a nucleoprotein that encapsulates the viral and the unsegmented negative-stranded RNA. The P gene produces a phosphoprotein, which is important not only for transcription and replication but also for interactions with cellular protein components during axoplasmic transport. The M gene codes for a matrix protein. The G gene produces a single transmembrane glycoprotein which is assembled as a trimeric spike. This glycoprotein is responsible for the initial binding during infection of susceptible cells and is the only target for virus-neutralizing antibodies. The L gene encodes a polymerase for RNA synthesis.[14,15]

Route of Transmission

Bites by rabid animals generally inoculate virus-laden saliva through the skin into muscle and subcutaneous tissues. Other inoculation routes are rare. Rabies virus entry occurs through wounds or direct contact with mucosal surfaces. The virus cannot cross intact skin. The risk of rabies infection by a bite (5%-80%) is at least 50 times greater than that by a scratch (0.1%-1%) Mortality after untreated bites by rabid dogs ranges from 38% to 57% and depends on the severity and location of the wound as well as on the presumed virus concentration in the saliva.[16]

Bat virus might be more infectious when inoculated superficially into the epidermis since it replicates more rapidly in non-neuronal cells and at lower temperatures than do dog rabies viruses. Percutaneous infection probably occurs during unnoticed skin contact, which may result in a minute bite. The contact with infected people could be a potential risk for their relatives and health workers when unprotected direct contact with secretions from a patient containing viable virus occurs. [1]7

The RV migrates along peripheral nerves (via the fast axonal transport system) towards the CNS at about 50-100 mm per day. This movement is strictly retrograde, which indicates infection is via sensory and motor nerves. Invasion of the CNS by the RV glycoprotein may not occur via the sensory nerve pathway.

The incubation period varies from 2 weeks to 6 years (average: 2 to 3 months) according to the amount of viral inoculum and the inoculation site. Bites on the head, face, neck and hands, particularly together with bleeding, offer the highest risk and are generally associated with a shorter incubation period. The RV can stay in the muscle tissue for long periods and in certain circumstances, its long persistence may provide an opportunity for host immune clearance and post-exposure treatment.[18]

Clinical Features[19]

Early clinical features of rabies are nonspecific prodromal symptoms and local neurological symptoms, including paresthesias, pain, and pruritus at the site of virus entry. Clinical presentation of rabies evolves into either encephalitic (furious) or paralytic (dumb) forms of the disease. Hyperexcitability, autonomic dysfunction, and hydrophobia are characteristic of encephalitic rabies, and quadriparesis with sphincter involvement is characteristic of paralytic rabies central nervous system involvement, such as headache, stiff neck, muscle spasm, urinary retention, paraesthesias, and difficulty in

walking, muscle spasm of the back or neck, reflex changes, urinary retention, muscle weakness of varying degree, and vague sensory changes. It may be accompanied by fever. In children rabies can be divided clinically into two stages:

Stage 1 (Lasts Two to 10 Days): fever, headache, not feeling well, decreased appetite, vomiting. pain, itching, or numbness and tingling at the site of the wound may occur.

Stage 2: difficulty in swallowing (sometimes referred to as "foaming at the mouth" due to the inability to swallow saliva), agitation and disorientation, paralysis may result in immediate death or coma resulting in death from other complications.[20]

Diagnosis

Rabies can be difficult to diagnose because, in the early stages, it is easily confused with other diseases or aggressiveness.[21] The reference method for diagnosing rabies is by performing PCR or viral culture on brain samples taken after death. The diagnosis can also be reliably made from skin samples taken before death.[22] Diagnosis can be made from saliva, urine, and cerebrospinal fluid samples, but this is not as sensitive. Cerebral inclusion bodies called Negri bodies are 100% diagnostic for rabies infection but are found in only about 80% of cases.

The differential diagnosis in a case of suspected human rabies may initially include any cause of encephalitis, in particular infection with viruses such as herpesviruses, enteroviruses, and arboviruses such as West Nile virus. The most important viruses to rule out are herpes simplex virus type one, varicella zoster virus, and (less commonly) enteroviruses, including coxsackie viruses, echoviruses, polioviruses, and human enteroviruses 68 to 71.[23]

Prevention[24]

Various strategies include:

- Vaccinating dogs, cats, rabbits, and ferrets against rabies
- Keeping pets under supervision
- Not handling wild animals or strays
- Contacting an animal control officer upon observing a wild animal or a stray, especially if the animal is acting strangely
- If bitten by an animal, washing the wound with soap and water for 10 to 15 minutes and contacting a healthcare provider to determine if post-exposure prophylaxis is required

September 28 is World Rabies Day, which promotes the information, prevention, and elimination of the disease

Treatment

Post Exposure Prophylaxis

Local Wound Management: Wounds should be treated and left open initially if they are punctures rather than lacerations, are not potentially disfiguring, are inflicted by humans, involve the legs and arms (particularly the hands) as opposed to the face, or occurred more than 6 to 12 hours earlier in the case of bites to the arms and legs and 12 to 24 hours earlier in the case of bites to the face. Facial lacerations from dog bites or cat bites are almost always closed. Because any foreign material in a contaminated wound increases the risk of infection, subcutaneous sutures should be used sparingly. Children may require sedation to allow adequate exploration, decontamination, and when indicated, repair of the wound. For bites on the hands and feet, placement of a proximal tourniquet often facilitates visualization of deep structures. Physicians may choose to re-evaluate wounds that were initially left open after 72 hours to determine whether delayed primary closure would be appropriate. Prophylactic antibiotics reduced the rate of infection.[25]

Rabies Vaccine

Antirabies vaccines are of 2 types-Neural and Non-neural vaccines

A. Neural Vaccine:[26-28]

1. Semple Vaccine was developed by Semple at Central Research Institute, Kasauli, and it has been the most

widely used vaccine for over half-a-decade. It is a 5% suspension of sheep brain infected with fixed virus and inactivated with phenol at 37°C.

2. Beta propionilactione vaccine (BPL) is a modification of the Semple vaccine in which BPL is used as an inactivating agent instead of phenol. It is believed to be more antigenic, so a smaller dose is required.
3. Suckling mouse brain vaccine was developed with the aim to reduce the encephelitogenic properties of the rabies vaccine. The infant mice (< 9 days old) are used for vaccine production. The amount of myelin in infant brain is scanty and this results in a lower incidence of neuroparalytic side effects.

Neuroparalytic complications of neural Vaccines include:

1 Meningoencephalitis
2. Meningoencephelomyelitis
3. Mononeuritis multiplex
4. Dorso-lumbar transverse myelitis
5. Ascending paralysis of Landry's type

B. Non-Neural Vaccine[29-33]

1 Primary Cell Culture Vaccines

a. Human Diploid Cell Vaccine (MIRV-HDC in India): the vaccine is prepared from Pitman Moore strain of rabies virus grown on MRC-5 human diploid cell culture line, concentrated by ultrafiltration and inactivated by BPL a) Intramuscular administration: a single dose vial containing lyophilised vaccine that is reconstituted in the vial with the accompanying diluent to a volume of 1 ml. b) Intradermal administration: a single dose syringe containing lyophilised vaccine

b. Purified Chick Embryo Cell Vaccine (PCECV- RabipurTm): PCECV is prepared from fixed rabies virus strain FLURY LEP grown in primary cultures of chicken fibroblasts It is available as a single dose vial containing lyophilised vaccine.

c. Purified Vero Cell Rabies Vaccine (PVCV – AbhayrabTm, VerorabTm): PVCV contains Wistar strain of virus, with the vero cell line as the substrate, which is a continuous cell line. The vaccine induces a good immune response after primary as well as secondary immunisation, the results being comparable to those of HDCV.

d. Rabies Vaccine Adsorbed (RVA): is prepared from Kissling strain of challenge virus standard (CVS) rabies virus adapted to foetal rhesus lung diploid cell culture. The vaccine virus is inactivated by BPL and concentrated by adsorption to aluminum phosphate. It is a liquid rather than lyophilised vaccine and is approved only for Intramuscular use as a 1 ml dose.

e. Primary Hamster Kidney Cell Vaccine (PHKCV): this vaccine is used in China and Russia locally. The virus is propagated in primary kidney cells of Syrian hamster.

Categorisation of Bites (WHO)

Category I: touching or feeding of animals or licks on intact skin. In such a case if the history is reliable, no treatment is required as there is no exposure to the rabies virus.

Category II: minor scratches or abrasions without bleeding, or licks on broken skin and nibbling of skin. This requires a full course of antirabies vaccine.

Category III: single or multiple transdermal bites or contamination of mucous membrane with saliva. In this case both immunoglobulin and vaccine should be used.

Schedule for Post-Exposure Vaccination[34]

Traditionally, modern cell culture vaccines

are given intramuscularly. The vaccines should not be administered in the gluteus muscle to avoid injury to the sciatic nerve and to lessen the delivery of vaccine to the adipose tissue. Two regimens are used:

(a). Classic 5 dose intramuscular regimen (Essen regimen) in which one dose of vaccine, i.e., 1 ml of HDCV, PCECV or 0.5 ml of PVCV is administered on day 0, 3, 7, 14, and 28.

(b). Alternate 2 - 1 - 1 regimen in which 2 doses of vaccine are given on both deltoids on day 0 and then one dose each on day 7 and 21.

Antirabies Serum (ARS)/Rabies Immunoglobulin (RIG) Treatment[35,36]

1. *ARS or Equine Rabies Immunoglobulin (ERIG):* Potent antirabies serum has been prepared in horse and other animals. ERIG is widely used in India. It should be given as early as possible, preferably on day 0 treatment. It should never be given alone without concomitant use of antirabies vaccine. It can be given within 7 days of starting antirabies vaccine. Dose of ERIG is 40 IU/Kg of body weight. As much as possible ERIG should be infiltrated around and into the wound(s), even if the lesion has begun to heal. If the calculated dose of ERIG is insufficient, then sterile saline can be used to dilute it 2 - 3 times to permit thorough infiltration. Any remaining ERIG is injected intramuscularly at a site distant from the site of vaccine administration.
2. *Human Rabies Immunoglobulin (HRIG):* HRIG has replaced ERIG in most developed countries. In developing countries, the use is limited because of prohibitively high costs of HRIG. The dose is 20 IU/Kg body weight and use is similar to ERIG. It is free from anaphylactic and serum sickness like adverse effects.

Henry Wilde, Siriwan Sirikawin studied that failures of postexposure treatment of rabies in which tissue culture-derived vaccines and immune globulins had been used treatment failures involving children who suffered severe face, head, neck, and arm injuries when attacked by a rabid dog. Surgical wound cleansing and primary treatment with rabies immune globulin (RIG) and a series of potent tissue-culture vaccine injections had been started within 3 days following the attacks. A hypothesis concerning possible causes of these treatment failures and recommendations for improvements in the management of cases of severe and multiple bites in small children are presented.[37-39]

As children living in rabies endemic countries are at particular risk of being exposed, it is important to target this population. Modern cell culture rabies vaccines like human diploid cell vaccine (HDCV), purified Vero cell rabies vaccine (PVRV), purified duck embryo vaccine (PDEV) or purified chick embryo cell vaccine (PVRV) are licensed for PrEP and can be used in children. Good immunogenicity and favorable tolerability and safety have been demonstrated in clinical trials using HDCV ,PVRV and PCECV. PCECV was demonstrated to be safe and immunogenic when given IM to children up to 15 y of age. Regardless of the route of administration (IM or ID), VNA concentrations reached levels above 0.5 IU/mL, which is regarded as an adequate immune response after vaccination. This was independent of the age when PrEP was administered. To date, no difference was seen in the immune response of toddlers, school-aged children or adolescents. Failures in reaching adequate VNA have not been reported in healthy individuals. The only documented cases of PrEP seroconversion failures have been observed in immunocompromised persons. HIV-infected children did not respond well to IM PrEP with HDCV, where the immune response correlated with the CD4+ T-cell levels.[40-45]

Conclusion

Rabies is a fatal viral disease transmitted from animals to humans. It causes more than 35,000 human deaths per year. Rabies virus entry occurs through wounds or direct contact with mucosal surfaces.Children should be kept away from animals as they are prone to bite. Prophylaxis in children against rabies is same as in adults. Mortality after untreated bites by rabid dogs ranges from 38% to 57%. According to presentation, it can be confused with many diseases, so a clinician should be vigilant. Proper use of immunoglobulin and post and pre – exposure prophylaxis can reduce the incidence an complications of disease by great extent. Now a days, purified cell culture vaccines are available with much less side effects than neural vaccines. Also, pets kept at home should be regularly vaccinated against it.

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