Rabies, human
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Rabies, human

Overview

Lyssaviruses infect the central nervous system, causing encephalitis and ultimately death. Early symptoms of rabies in humans are nonspecific, consisting of fever, headache, and general malaise. As the disease progresses, neurological symptoms appear and may include insomnia, anxiety, confusion, slight or partial paralysis, excitation, hallucinations, agitation, hypersalivation, difficulty swallowing, and hydrophobia (fear of water). Death usually occurs within days of the onset of symptoms, although treatment may increase the length of survival and very rarely result in recovery.[1] Under extremely rare occasions, abortive infection with rabies may occur.[2] In addition to diagnostic testing for rabies, these cases require extensive medical investigation to rule-out other possible etiologies responsible for the patient's illness.

The number of rabies-related human deaths in the United States declined from more than 100 annually in 1900 to an average of two to three a year in the past decade (2000–2009). The administration of a standard regimen of postexposure prophylaxis (PEP) to persons exposed to rabies has proven extremely successful in preventing the disease. In the United States, human fatalities from rabies occur in people who fail to seek medical assistance and PEP, usually because they were unaware of the need to seek medical attention, or occasionally, not aware that an exposure may have occurred.

The incubation period of rabies in people is variable (depending upon factors such as the site and severity of the bite), but averages three to eight weeks. Rabies in humans is 100% preventable through prompt appropriate medical care. Following an exposure to rabies, there is normally a window of opportunity (usually measured in days) in which the patient can receive a series of shots to keep him/her from developing the disease. In 2008, a human rabies fatality occurred in Missouri in an individual who did not seek medical advice or treatment following a bat bite.[3] Before this, the last human rabies infection in the state was reported in 1959.

For a more complete description of human rabies, refer to the following texts:[4,5,6,7]

- Control of Communicable Diseases Manual (CCDM).
- Red Book, Report of the Committee on Infectious Diseases.
- Human Rabies Prevention - United States, 2008. Recommendations of the Advisory Committee on Immunization Practices.
- Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies. Recommendations of the Advisory Committee on Immunization Practices.

2011 Case Definition – Rabies, human[8] - (1/14)

Clinical description
Rabies is an acute encephalomyelitis that almost always progresses to coma or death within 10 days after the first symptom.

Laboratory criteria for diagnosis
- Detection of Lyssavirus antigens in a clinical specimen (preferably the brain or the nerves surrounding hair follicles in the nape of the neck) by direct fluorescent antibody test, or
- Isolation (in cell culture or in a laboratory animal) of a Lyssavirus from saliva or central nervous system tissue, or
- Identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the CSF, or
- Identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the serum of an unvaccinated person, or
- Detection of Lyssavirus viral RNA (using reverse transcriptase-polymerase chain reaction [RT-PCR]) in saliva, CSF, or tissue.

Case classification
Confirmed: A clinically compatible case that is laboratory confirmed by testing at a state or federal public health laboratory.

Comment
Laboratory confirmation by all of the above methods is strongly recommended.

Information Needed for Investigation

- **Rabies (human) is an "Immediately Reportable Disease"** in accordance with 19 CSR 20-20.020, *Reporting Communicable, Environmental and Occupational Diseases* and shall be reported to the local health authority or to the Department of Health and Senior Services (DHSS) immediately upon first knowledge or suspicion by telephone, facsimile or other rapid communication.
- **Verify the diagnosis.** Determine what laboratory tests were conducted and the results. Investigate any report of illness that meets any of the following criteria:
  - A person with one or more of the following clinical findings: encephalitis, myelitis, dysphagia, hydrophobia, anxiety, agitation, or paresthesias or pain at the wound site; AND one or more of the following laboratory findings:

- detection of Lyssavirus antigens in a clinical specimen (preferably the brain or the nerves surrounding hair follicles in the nape of the neck) by direct fluorescent antibody test;
- isolation (in cell culture or in a laboratory animal) of a Lyssavirus from saliva or central nervous system tissue;
- detection of Lyssavirus viral RNA (using reverse transcriptase-polymerase chain reaction [RT-PCR])in saliva, CSF, or tissue;
- identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the CSF.

▪ A person with one or more of the following clinical findings: encephalitis, myelitis, dysphagia, hydrophobia, anxiety, agitation, or paresthesias or pain at the wound site; AND no previous vaccination for rabies; AND identification of Lyssavirus specific antibody (i.e. by indirect fluorescent antibody (IFA) test or complete rabies virus neutralization at 1:5 dilution) in the person's serum.

Notification

- Contact the District Communicable Disease Coordinator, the Senior Epidemiology Specialist for the District, or MDHSS – Office of Veterinary Public Health (OVPH), phone (573) 526-4780, Fax (573) 751-6185, or for after hours notification contact the MDHSS' ERC at (800) 392-0272 (24/7) immediately if human rabies is suspected.
- If a case(s) is associated with a childcare center, OVPH or the LPHA will contact the Bureau of Environmental Health Services (BEHS), phone (573) 751-6095, Fax (573) 526-7377 and the Section for Child Care Regulation, phone (573) 751-2450, Fax (573) 526-5345.
- If a case(s) is associated with a long-term care facility, OVPH or the LPHA will contact the Section for Long Term Care Regulation, phone (573) 526-8524, Fax (573) 751-8493.
- If a case is associated with a hospital, hospital-based long-term care facility, or ambulatory surgical center, OVPH or the LPHA will contact the Bureau of Health Services Regulation phone (573) 751-6303, Fax (573) 526-3621.

Control Measures

- **Public education remains an important part of rabies prevention**. Although rabies is a fatal disease that has no known cure, it is preventable with timely and proper administration of rabies postexposure prophylaxis. Public education should emphasize avoiding exposure to bats and other potentially rabies-infected wildlife and the importance of proper wound care and seeking prompt medical attention after potential exposures from such animals. (e.g. Any person who has been bitten, scratched, or somehow exposed to the saliva of a potentially rabid animal should see a physician as soon as possible for postexposure treatment).

- Vaccinate your pets (dogs, cats, ferrets) and livestock (sheep, cattle, horses) against rabies.
- Don't let your pets wander unsupervised.
- Spay or neuter your pets; pets that are fixed are less likely to leave home and become strays.

An excellent informational sheet, Rabies: Questions and Answers - *Information about the disease and vaccines* is available from the Immunization Action Coalition. Additional resources are also available on CDC's website at: http://www.cdc.gov/rabies/ and http://www.cdc.gov/vaccines/vpd-vac/rabies/default.htm.

- **Postexposure prophylaxis is recommended** for persons who have been bitten by probable or confirmed rabid animals, or whose mucous membranes or fresh open wounds (including scratches) have come into contact with the animal's saliva.
- Hospital contacts who were bitten, or whose mucous membranes or fresh open wounds (including scratches) have come in contact with saliva, cerebrospinal fluid (CSF), or brain tissue of a human patient with rabies should receive postexposure prophylaxis. (Note: Exposure to a human with rabies has not been documented in the United States as a means of rabies transmission, except after tissue/organ transplantation from donors who died of unsuspected rabies.) Casual contact with an infected person (e.g., by touching a patient) or contact with noninfectious fluids or tissues (e.g., urine, blood, or feces) alone does not constitute an exposure and is not an indication for prophylaxis.
- Special consideration should be given to individuals who report a potential encounter with a bat, since transmission of rabies virus may occur from minor, seemingly unimportant, or unrecognized bites from bats. There are usually only one or two human rabies cases per year in the United States, with the most common source of the rabies virus being bats. Among the 34 naturally acquired cases of rabies in humans in the United States from 1990-2007, 23 (68%) were associated with bats while in 11 (32%) cases no bat encounter was reported (presumably because the bite was undetected or detected but not reported).[6]
- Rabies Postexposure Prophylaxis (RPEP) – Medical providers should utilize all recommendations regarding administration of RPEP as provided by the Centers for Disease Control and Prevention (CDC).[6,7] Generally, RPEP should always include administration of both passive antibody and vaccine, with the exception of persons who have ever previously received complete vaccination regimens (pre-exposure or post-exposure) with a cell culture vaccine or persons who have been vaccinated with other types of vaccines and have previously had a documented rabies virus neutralizing antibody titer. These persons should receive only vaccine (i.e., postexposure for a person previously vaccinated). The combination of human rabies immunoglobulin (HRIG) and vaccine is recommended for both bite and nonbite exposures reported by persons who have never been previously vaccinated for rabies, regardless of the interval between exposure and initiation of prophylaxis. If postexposure prophylaxis has been initiated and

appropriate laboratory diagnostic testing (i.e., the direct fluorescent antibody test) indicates that the exposing animal was not rabid, RPEP can be discontinued.

- Rabies Immunoglobulin Use: HRIG is administered only once (i.e., at the beginning of antirabies prophylaxis) to previously unvaccinated persons to provide immediate, passive, rabies virus neutralizing antibody coverage until the patient responds to human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) by actively producing antibodies. If HRIG was not administered when vaccination was begun (i.e., day 0), it can be administered up to and including day seven of the postexposure prophylaxis series. Beyond the seventh day, HRIG is not indicated because an antibody response to cell culture vaccine is presumed to have occurred. Because HRIG can partially suppress active production of antibody, the dose administered should not exceed the recommended dose. The recommended dose of HRIG is 20 IU/kg (0.133 mL/kg) body weight. This formula is applicable to all age groups, including children. If anatomically feasible, the full dose of HRIG should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected intramuscularly (IM) at a site distant from vaccine administration. This recommendation for HRIG administration is based on reports of rare failures of postexposure prophylaxis when less than the full amount of HRIG was infiltrated at the exposure sites. HRIG should never be administered in the same syringe or in the same anatomical site as the first vaccine dose. However, subsequent doses of vaccine in the five-dose series can be administered in the same anatomic location where the HRIG dose was administered, if this is the preferable site for vaccine administration (i.e., deltoid for adults or anterolateral thigh for infants and small children).
- Vaccine Use: Two rabies vaccines are available for use in the United States (Table 1).[6] Either can be administered in conjunction with HRIG at the beginning of post-exposure prophylaxis. A regimen of four one-mL doses of HDCV or PCECV should be administered IM to previously unvaccinated persons. The first dose of the four-dose course should be administered as soon as possible after exposure. This date is then considered day 0 of the postexposure prophylaxis series. Additional doses should then be administered on days 3, 7, and 14 after the first vaccination. A fifth dose of vaccine should be administered on day 28 for persons with altered immunocompetence. Previously vaccinated persons should receive two doses of HDCV or PCECV three days apart following exposure to a known or potentially rabid animal (HRIG should not be given to these persons). For adults, the vaccination should always be administered IM in the deltoid area. For children, the anterolateral aspect of the thigh is also acceptable. The gluteal area should never be used for HDCV or PCECV injections because administration of HDCV in this area results in lower neutralizing antibody titers.
- Sources of Human Rabies Vaccine and Immunoglobulin: Human rabies vaccine and HRIG are usually readily available through hospital and clinic pharmacies which medical providers normally utilize. These products may also be accessed from

"sister" facilities located in the same medical/hospital chain. Providers can order vaccine and HRIG directly from manufacturers listed in Table 1 of CDC's *Human Rabies Prevention - United States, 2008. Recommendations of the Advisory Committee on Immunization Practices.*[6] These products can usually be obtained by "overnight" delivery.

Programs for Uninsured and Underinsured Patients[9]

Patient assistance programs that provide medications to uninsured or underinsured patients are available for rabies vaccine and immune globulin.

Sanofi Pasteur's Patient Assistance Program (providing Imogam ® Rabies-HT and Imovax ® Rabies as well as other vaccines) is now administered through the Franklin Group. A healthcare professional or patient can either contact the Franklin Group directly, or call the customer service team (1-800-VACCINE) who will transfer them to the Franklin Group. The Franklin Group will review the application against the eligibility criteria. For more information about the program or to request an application, please contact the Sanofi Pasteur, Inc. Patient Assistance Program (Franklin Group) at 1 (866) 801-5655. Instructions and request forms are available at the Sanofi Patient Connection website.

Novartis' Patient Assistance Program for RabAvert ® is managed through RX for Hope and can be accessed at 1-800-589-0837. Instructions and request forms are available at the Rx for Hope website RabAvert Patient Assistance Program.

Control Measures

- See the Control of Communicable Diseases Manual, Rabies (Hydrophobia), "Methods of control."[4]
- See the Red Book, Rabies, "Control Measures."[5]
- See Human Rabies Prevention - United States, 2008 Recommendations of the Advisory Committee on Immunization Practices.[6]

Laboratory Procedures

Human Specimens:

Requests for rabies diagnosis in humans should be coordinated with the Office of Veterinary Public Health (573) 526-4780 (after hours 1-800-392-0272) and the State Public Health Laboratory (SPHL) (573) 751-3334. The following four specimens are generally all required: saliva, blood, CSF, nuchal biopsy (skin on the back of the neck). Information regarding testing of human specimens can be found at http://health.mo.gov/lab/rabies.php. In addition, the CDC link for information regarding specimen collection is: http://www.cdc.gov/rabies/specific_groups/doctors/ante_mortem.html (this page includes a link to the specimen submission form). Information from CDC regarding diagnostic procedures may be found at http://www.cdc.gov/rabies/specific_groups/doctors/index.html.

Reporting Requirements

Rabies (human) is an "Immediately Reportable Disease" and shall be reported to the local health authority or to MDHSS immediately upon first knowledge or suspicion by telephone, facsimile or other rapid communication. The MDHSS may be contacted afterhours through the MDHSS/ERC by calling (800) 392-0272 (24/7).

As a Nationally Notifiable Condition, **confirmed** human rabies cases are an **IMMEDIATE, URGENT** report to the Centers for Disease Control and Prevention (CDC). **IMMEDIATE, URGENT** reporting requires MDHSS to call the CDC EOC at 770-488-7100 within 24 hours of a case meeting the notification criteria; followed by submission of an electronic case notification via (WebSurv) in the next regularly scheduled electronic transmission.

1. Health care providers should **immediately** report any suspected human rabies case to the local health agency of the patient's residence or MDHSS.
2. For confirmed cases complete a "Disease Case Report" (CD-1) and send the completed form to the DHSS District Health Office.
3. Entry of the completed CD-1 into the WebSurv database negates the need for the paper CD-1 to be forwarded to the District Health Office.
4. MDHSS will report to CDC following the above reporting criteria (see box).
5. All outbreaks or "suspected" outbreaks must be reported as soon as possible (by phone, fax, or e-mail) to the District Communicable Disease Coordinator. This can be accomplished by completing the Missouri Outbreak Surveillance Report (CD-51).
6. Within 90 days of the conclusion of an outbreak, submit the final outbreak report to the District Communicable Disease Coordinator.

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Web Resources and Information

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3. CDC "Rabies, Resources." Retrieved January 8, 2014 from: http://www.cdc.gov/rabies/resources/index.html.
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