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Rabies—Update on a Global Disease

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Rabies, a fatal viral zoonosis, persists in both developed and developing countries worldwide in spite of successful preventive public health measures and postexposure therapies. Considering the years of life lost, rabies ranks seventh among all infectious diseases in the world.[1] Public health campaigns, emphasizing rabies immunization of pets and development of effective pre- and postexposure immunization regimens, have reduced acquired human rabies-related fatalities in the U.S. to less than 3 per year.[2] These few cases almost always involve a bat variant of the rabies virus causing fatal encephalitis.[3]

Etiology. The RNA, neurotropic virus causing rabies has a bullet-shaped nucleocapsid surrounded by a lipoprotein envelope. The unique genetic patterns in the nucleocapsid and glycoprotein components of rabies virus isolates provide an opportunity through molecular techniques to identify reservoir hosts (eg, bat, dog, fox, raccoon, skunk) providing useful epidemiological data.[1]

Epidemiology. Each year, an estimated 55,000 people die of rabies in Africa and Asia where infection is endemic in dogs.[1] In contrast, only 19 indigenously acquired rabies-related human fatalities were reported in the U.S. from 2000 to 2006, 17 of which were associated with rabies virus variants maintained by bats.[3] Mass immunization of pet dogs and cats at an estimated annual cost of 300 million dollars in great part accounts for the low incidence of human rabies in the U.S.[1] Wildlife, primarily raccoons, skunks, bats and foxes, accounted for more than 92% of all animal rabies cases reported to the CDC in 2005.[3] Oral rabies vaccine projects are being evaluated to control rabies in wildlife in Texas, Florida, Alabama and Ohio with over 4.1 million baits distributed in July of 2006.[3]

Transmission. Transmission requires introduction of rabies virus from saliva or infected neural tissue into bite wounds or open cuts in skin or mucous membranes.[4] Minor, possibly unrecognized bites from bats (contributing to inaccurate recall), appear to have played a role in recent human fatalities in the U.S.[4] Human to human transmission of rabies has been described in 8 patients receiving corneal transplants[4] and, recently, 4 U.S. patients receiving organ transplants (lung, liver, and kidney) from one donor, raising new questions about tissue tropism and rabies screening of organ and tissue donors.[5]

Clinical Signs. The incubation period ranges from 2 weeks to 6 years, averaging 2 to 3 months, depending upon inoculum and proximity to the brain.[2] Viral replication at dorsal root ganglion causes the first clinical sign of neuropathic pain near the inoculation site.[2] The virus migrates to the central nervous system at 15–100 mm per day and then outward within peripheral nerves infecting adjacent organs such as salivary glands with viral shedding in saliva.[2] Two clinical presentations, furious form (anterior horn cell dysfunction) and paralytic form (peripheral nerve dysfunction), lead to death within 5 days without intensive care.[2]

Diagnosis. Diagnosis based on clinical signs of phobic spasms (hydro- or aerophobia), paralytic or Guillaine–Barre-like syndrome, or excitation is difficult and unreliable especially considering that typical or nonclassic rabies is being increasingly recognized.[2] Magnetic resonance imaging, specifically hypersignal T2 images in brainstem, hippocampus, hypothalamus, deep subcortical and cortical white and gray matter, respectively, as well as gadolinium enhancement contribute to a rabies diagnosis. Antigen detection using fluorescent antibody test in skin biopsies taken from

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the nuchal area has proven to be a useful diagnostic tool especially early in the disease.[2] The success rate of virus isolation performed on saliva, tears, cerebrospinal fluid may be impacted by antibody status and viral shedding.[2] Rabies antibodies in serum and infrequently in CSF may be detected by various tests (ELISA, RFFIT, FAVN) approximately 8 days after onset of symptoms.[2] Molecular techniques such as PCR and nucleic acid sequence based amplification may detect viral RNA in saliva, CSF, tears, skin biopsies and urine and may be useful in combination with more conventional tools.[2,6] Postmortem fluorescent antibody testing of brain tissue and virus isolation in cell culture confirm a diagnosis.[2]

Treatment. Administration of postexposure prophylaxis (PEP) requires risk assessment including evaluation of the suspected rabid animal and circumstances of exposure.[2,4] PEP should not be initiated in cases involving a healthy dog, cat or ferret in the U.S. unless clinical signs of rabies occur in the animal over a 10-day observation period.[4] Consultation with public health officials regarding immediate PEP administration is recommended if the animal (dog, cat, ferret, skunk, raccoon, fox, bat) is suspected to be rabid or not available for testing. Suspect exposures from other mammals (eg, livestock, woodchucks, other wildlife) should be evaluated case by case in consultation with public health officials.[4]

Treatment begins with 15 minutes of thorough washing of bite wounds and scratches with soap, water and preferably a virucidal agent such as povidone iodine.[4] PEP in an unvaccinated person includes administration of passive antibody, Rabies Immune Globulin (RIG), at 20 IU/kg infiltrated around the wound distant from the vaccine administration.[4] One of 3 inactivated vaccines (human diploid cell vaccine, HDCV; rabies vaccine adsorbed, RVA; or purified chick embryo cell vaccine, PCEC) should be administered in a 1.0 mL dose intramuscularly in the deltoid region (never gluteal) on day 0, 3, 7 14 and 28. Treatment of a previously vaccinated person (eg, veterinarian, wildlife biologist) includes wound cleansing, no RIG and 2 1.0 mL doses of vaccine administered on day 0 and 3.[4]

More affordable or available alternative PEP agents such as monoclonal antibody, human polyclonal immune globulin, and intradermal route of smaller doses of vaccine are under consideration given limited supply of vaccine and human rabies immunoglobulin especially in areas of the world where canine rabies is endemic, human mortality is high and access to treatment is limited.[7–9]

Postexposure treatment, not included in the recommendations of the CDC Advisory Committee on Immunization Practices,[4] involving induction of a therapeutic coma without vaccine or RIG administration has been described in 5 patients with clinical rabies resulting in one survival.[10–12] The benefits of this regimen should be further explored in cell culture systems and animal models of rabies to potentially develop additional therapeutic approaches.[12]

Prevention. The preponderance of bat-related, human rabies fatalities in the U.S. underscores the need for elevating public awareness, most importantly in children, of the risk after contact with bats and other wildlife.[11] Wildlife, especially bats, should never be handled and should be kept away from living quarters and public places.[11] Persons bitten by a potentially rabid animal or directly contacting a bat should immediately: (1) wash any wound with soap and water, (2) safely capture the animal (without direct contact) for testing, and (3) contact public health officials and a physician for evaluation for PEP.

People at-risk of occupational exposure (eg, rabies laboratory workers, veterinarians, animal control officers) may receive pre-exposure prophylaxis considering their risk category.[4] Primary immunization with 1.0 mL of HDCV, RVA or PCEC given intramuscularly (deltoid area) on day 0, 7 and 21 or 28 or 0.1 mL of HDCV given intradermally on day 0, 7 and 21 or 28 may be followed by timely boosters and/or serum antibody titers considering risk category.[4]

SUMMARY. Rabies infection is nearly always fatal without appropriate treatment.[2,4,11] Even though the incidence in the U.S. is low, rabies should be considered in the differential diagnosis of any patient presenting with encephalitis.[2] A timely diagnosis of rabies and administration of PEP may be life saving. The cornerstone of rabies prevention in the U.S. remains immunization of pet dogs and cats. The prevalence of rabies in North American wildlife however requires efforts by physicians, veterinarians, educators and community leaders to elevate public awareness of the rabies risk associated with contacting wildlife, especially bats.

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