



Rabies Virus

Encyclopedia of the Neurological Sciences
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RABIES VIRUS is a highly neurotropic virus that causes an acute and fatal infection of the central nervous system (CNS). The virus is normally transmitted by biting animals, although transmission has rarely been documented from aerosolized virus in caves and laboratories and by corneal transplantation. Although there is no effective treatment for rabies, the disease is preventable if current guidelines are followed after an exposure.

VIROLOGY

Rabies virus is a RNA virus in the Rhabdoviridae family (genus *Lyssavirus*), and the genome is single stranded, negative sense, and nonsegmented. Virus particles are bullet shaped with an envelope covered with surface glycoprotein projections, which appear as spikes. The glycoprotein is the major surface antigen of the virus. It induces and binds virus-neutralizing antibodies and is important for immunity.

PATHOGENESIS

Rabies virus is inoculated into muscle and subcutaneous tissues in the saliva of a biting animal (Fig. 1). There is a delay in movement of the virus at the site of inoculation during the incubation period that lasts for weeks to months. Rabies virus binds to nicotinic acetylcholine receptors at the neuromuscular junction and travels toward the spinal cord within axons of peripheral nerves by retrograde fast axonal transport

at a rate of approximately 50–100 mm per day. The virus disseminates within axons in the CNS along neuroanatomical pathways. Rabies virus replicates in neurons and causes neuronal dysfunction by uncertain mechanisms, which is likely responsible for the clinical features and fatal outcome of the disease. Behavioral changes occur in rabies that lead to transmission by biting. Subsequently, there is centrifugal (away from the CNS) spread along nerves to multiple organs,

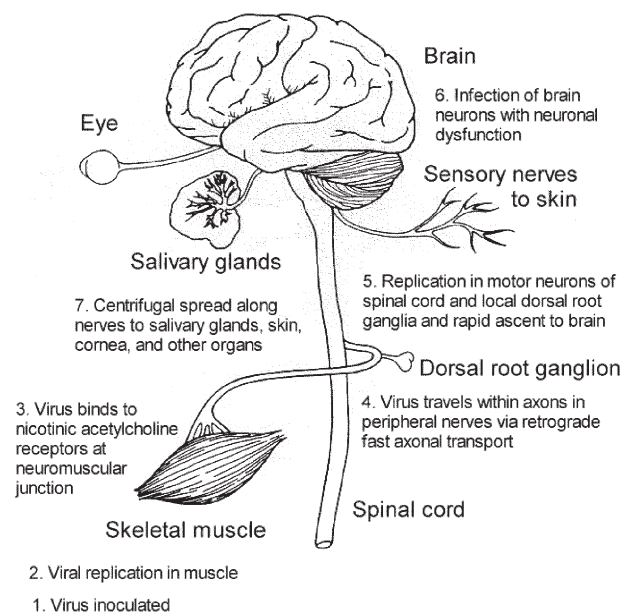


Figure 1
Schematic representation of the pathogenetic steps after peripheral inoculation of rabies virus [adapted with permission from Robinson, P. A. (1991). Rabies virus. In *Textbook of Human Virology* (R. B. Belshe, Ed.), 2nd ed., pp. 517–540. Mosby-Year Book, St. Louis].

including the salivary glands in animals that transmit the virus. Rabies virus is secreted in the saliva in vectors and transmission occurs to other hosts by biting. Bats, raccoons, skunks, and foxes are important rabies vectors in North America, and dogs are most important worldwide.

CLINICAL MANIFESTATIONS

The incubation period in rabies is usually 20–90 days following an exposure, but it may occasionally extend over a year. Early symptoms of rabies are nonspecific and include headache, malaise, anorexia, and nausea. The earliest neurological symptoms are numbness and tingling at the site of the bite (the bite wound has usually healed by this time), which may reflect infection in local dorsal root ganglia. There are two clinical forms of rabies: a classic or encephalitic form in 80% of patients and a paralytic form in 20% of patients. In classic rabies, there are periods of hyperexcitability lasting minutes separated by lucid periods. Autonomic dysfunction, including hypersalivation, gooseflesh, cardiac arrhythmias, and priapism in males, is common. Fever is usually present. Many patients have hydrophobia with spasms of pharyngeal and inspiratory muscles, including the diaphragm, on attempts to drink. This becomes a conditioned reflex and even the sight of water may precipitate the spasms. The neurological illness is progressive, and patients may become comatose and develop failure of multiple organ systems. Death usually occurs in a few days, but life may be prolonged by aggressive care of complicating medical problems in an intensive care unit. In paralytic rabies, patients develop flaccid weakness that often initially involves the bitten extremity and progresses to weakness of all limbs (quadriplegia) with impairment of bladder function. Patients with paralytic rabies may survive longer than patients with classic rabies. Paralytic rabies may be misdiagnosed as Guillain–Barré syndrome.

DIAGNOSIS

Rabies should be strongly suspected if there is a history of an animal bite that is followed by a typical neurological illness, but patients may develop rabies without a history of an exposure and in the United States these cases are usually due to transmission from bats. Serum-neutralizing antibodies against rabies virus may not appear for several days after the onset of neurological illness, and they may not be

found prior to death. Electroencephalograms and imaging techniques (computed tomography and magnetic resonance imaging) do not usually show specific findings in rabies. Cerebrospinal fluid (CSF) may show a mononuclear pleocytosis. Rabies virus antigen detection in skin biopsies taken from the nape of the neck or in corneal impression smears is useful for an antemortem diagnosis of rabies. Rabies virus RNA may be detected in saliva, CSF, or in a skin biopsy using polymerase chain reaction amplification. Brain biopsies are performed infrequently and brain tissue may show characteristic pathological changes with cytoplasmic inclusions called Negri bodies, rabies virus antigen in neurons, and infectious rabies virus that can be cultured.

TREATMENT

There is no effective treatment for rabies after the neurological disease has developed, and the only survivors were immunized against rabies virus prior to the onset of their neurological disease. Both experimental antiviral therapy and immunotherapies have been unsuccessful.

PREVENTION

Rabies can be prevented following an exposure if current guidelines, which are published in the *Morbidity and Mortality Weekly Report* and available on the Internet at <http://www.cdc.gov/mmwr>, are carefully followed. A decision to initiate rabies postexposure prophylaxis (PEP) is based on details of the exposure, the species of animal, the animal's availability for observation or laboratory testing, and the local epidemiological situation. Algorithms can be helpful in making management decisions concerning rabies PEP (Fig. 2). Consultation with public health officials is important. Healthy dogs, cats, or ferrets may be closely observed and if they remain healthy for a period of 10 days, then rabies PEP is not necessary. PEP must not be delayed during observation of other animals.

Local wound cleansing is important in order to inactivate infectious rabies virus at the site of entry. Cleaning with soap and water is very useful and the use of virocidal agents is important for deeper wounds. A combination of active and passive immunization should be used in previously unimmunized individuals with a rabies exposure. Five doses of rabies vaccine (human diploid cell vaccine, purified chick embryo cell vaccine, or rabies vaccine

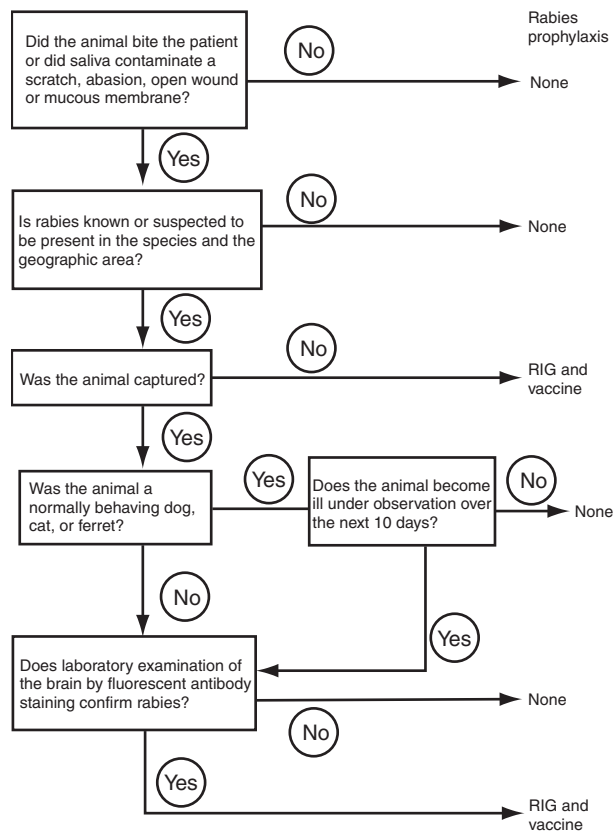


Figure 2 Algorithm for rabies postexposure prophylaxis [adapted with permission from Corey, L. (1998). Rabies virus and other rhabdoviruses. In *Harrison's Principles of Internal Medicine* (A. S. Fauci, E. Braunwald, K. J. Isselbacher, et al., Eds.), 14th ed., pp. 1128–1132. McGraw-Hill, New York].

adsorbed) should be given intramuscularly in the deltoid muscle on Days 0, 3, 7, 14, and 28. Passive immunization includes administration of 20 IU/kg of human rabies immune globulin (RIG) on Day 0. As much RIG as anatomically feasible should be infiltrated into and around the wounds, and any remaining volume should be given intramuscularly (gluteal area or lateral thigh muscles).

—Alan C. Jackson

See also—Adenoviruses; Central Nervous System Infections, Overview; Encephalitis, Viral; Enteroviruses; Measles Virus, Central Nervous System Complications of; Viral Vaccines and Antiviral Therapy

Further Reading

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Radiation Therapy and Chemotherapy, Neurological Complications of

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CANCER TREATMENT often requires several treatment modalities, among which radiation therapy (RT) and chemotherapy play central roles. Unfortunately, their efficacy is often diminished by neurotoxicity, which may be intensified when the modalities are combined. Disorders resulting from treatment-related neurotoxicity represent a major issue in neurooncology because they are frequent and the consequences can diminish the patient's quality of life. In some cases, they can even be life threatening and overshadow an otherwise good prognosis.

NEUROLOGICAL COMPLICATIONS OF RADIOTHERAPY

The wide distribution of the nervous system (central and peripheral) means that nervous tissue is always included within a radiation field even when the tumor does not affect nervous tissue. Thus, the brain may be affected during radiotherapy of head and neck cancer, the spinal cord during treatment of lung cancers, and the brachial plexus during irradiation of breast tumors. It has become clear that neural tissues are much more radiosensitive than previously thought, and among the main parameters taken into account for treatment planning (volume, total dose, dose per fraction, and duration of irradiation), the nervous system is most sensitive to the dose per fraction. With respect to neurotoxicity, the therapeutic index is very low for a number of tumors, meaning that the dose required for tumor control is