# 106 - 214 Rabies and Other Rhabdovirus Infections

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Rabies and Other

Rhabdovirus Infections PART 5 Infectious Diseases RABIES Rabies is a rapidly progressive, acute infectious disease of the central nervous system (CNS) in humans and animals that is caused by infection with rabies virus. The infection is normally transmitted from animal vectors via a bite exposure. Rabies has encephalitic and paralytic forms that progress to death. ■ ■ETIOLOGIC AGENT Rabies virus is a member of the family Rhabdoviridae. Two genera in this family, Lyssavirus and Vesiculovirus, contain species that cause FIGURE 214-1 Distribution of global rabies vectors. (Courtesy of the Centers for Disease Control and Prevention.)

human disease. Rabies virus is a lyssavirus that infects a broad range of mammals and causes serious neurologic disease when transmit ted to humans. This single-strand RNA virus has a nonsegmented, negative-sense (antisense) genome that consists of 11,932 nucleotides and encodes five proteins: nucleocapsid protein, phosphoprotein, matrix protein, glycoprotein, and a large polymerase protein. Rabies virus variants, which can be characterized by distinctive

nucleotide sequences, are associated with specific animal reservoirs. Six other non–rabies virus species in the Lyssavirus genus have been reported to cause a clinical picture similar to rabies. Vesicular stomatitis virus, a vesiculovirus, causes vesiculation and ulceration in cattle, horses, and other animals and causes a self-limited, mild, systemic illness in humans (see “Other Rhabdoviruses,” below). ■ ■EPIDEMIOLOGY Rabies is a zoonotic infection that occurs in a variety of mammals throughout the world except in Antarctica and on some islands. Rabies virus is usually transmitted to humans by the bite of an infected animal. Worldwide, endemic canine rabies is estimated to cause 59,000 human deaths annually. Most of these deaths occur in Asia and Africa, with rural populations and children disproportionally affected. Thus, in many resource-poor and resource-limited countries, canine rabies continues to be a threat to humans. However, in Latin America, rabies control efforts in dogs have been quite successful in recent years. Endemic canine rabies has been eliminated from the United States and most other resource-rich countries. Rabies is endemic in wildlife species, and a variety of animal reservoirs have been identified in different countries of the world (Fig. 214-1). Surveillance data from 2021 identified 3579 confirmed animal cases of rabies in the United States and Puerto Rico. Only 9.6% of these cases were in domestic animals, including 222 cases in cats,

50 in dogs, and 42 in cattle. In North American wildlife reservoirs, includ ing bats, raccoons, skunks, and foxes, the infection is endemic, with involvement of one or more rabies virus variants in each reservoir species (Fig. 214-2). “Spillover” of rabies to other wildlife species and to domestic animals occurs. Bat rabies virus variants are present in every state except Hawaii and are responsible for most indigenously acquired human rabies cases in the United States. Raccoon rabies is endemic along the entire eastern coast of the United States. Skunk rabies is present in the midwestern states, with another focus in California. Rabies in foxes occurs in New Mexico, Arizona, and Alaska. In the United States, there were five human rabies deaths in 2021 and none in 2019, 2020, and 2022. In Canada and Europe, epizootics of rabies in red foxes have been well controlled with the use of baits containing rabies vaccine. A similar approach, along with additional measures, is used in Canada to control incursions of raccoon rabies from the United States.

FIGURE 214-2 Distribution of the major rabies virus variants among wild terrestrial reservoirs in the United States and Puerto Rico, 2017–2021. Darker shading indicates counties with confirmed animal rabies cases in the past 5 years; lighter shading represents counties bordering enzootic counties without animal rabies cases that did not satisfy criteria for adequate surveillance. Small nonenzootic areas with no rabies cases reported in the past 15 years are shaded if they are in the vicinity of known enzootic counties and do not satisfy criteria for adequate surveillance. ARC FX rabies virus variant, Arctic fox RVV; AZ FX, Arizona fox RVV; CA SK, California skunk RVV; ERC, Eastern raccoon RVV; MG, Dog-mongoose RVV; NC SK, North central skunk RVV; SC SK, South central skunk RVV. (Reproduced with permission from X Ma et al: Rabies surveillance in the United States during 2021. J Am Vet Med Assoc 261:1045, 2023.) Rabies virus variants isolated from humans or other mammalian species can be identified by reverse-transcription polymerase chain reaction (RT-PCR) amplification and sequencing or by characteriza tion with monoclonal antibodies. These techniques are helpful in human cases with no known history of exposure. Worldwide, most human rabies (~99%) is transmitted from dogs in countries with endemic canine rabies and dog-to-dog transmission, and human cases can be imported by travelers returning from these regions. In North America, indigenously acquired human disease is usually associated with transmission from bats; there may be no known history of bat bite or other bat exposure in these cases. Most human

cases are due to a bat rabies virus variant associated with silver-haired and tricolored bats and, less commonly, from Brazilian (Mexican) free-tail bats. These are small bats whose bite may not be recognized, and the virus has adapted for replication at skin temperature and in cell types that are present in the skin. Transmission from nonbite exposures is relatively uncommon. Aerosols generated in the laboratory or in caves containing millions of Brazilian free-tail bats have rarely caused human rabies. Transmission has resulted from corneal transplantation and also from solid-organ transplantation and a vascular conduit (for a liver transplant) from undiagnosed donors with rabies in Texas, Florida, Germany, Kuwait, Syria, and China. Human-to-human transmission is extremely rare, although hypothetical concern about transmission to health care work ers has prompted the implementation of barrier techniques to prevent exposures from patients with rabies. ■ ■PATHOGENESIS The incubation period of rabies (defined as the interval between expo sure and the onset of clinical disease) is usually 20–90 days, but in rare

CHAPTER 214 Rabies and Other Rhabdovirus Infections cases is either as short as a few days or >1 year. During most of the incubation period, rabies virus is thought to be present at or close to the site of inoculation (Fig. 214-3). In muscles, the virus is known to bind to nicotinic acetylcholine receptors on postsynaptic membranes at neuromuscular junctions, but the exact details of viral entry into the skin and subcutaneous tissues have not yet been clarified. Rabies virus spreads centripetally along peripheral nerves toward the spinal cord or brainstem via retrograde fast axonal transport (rate, up to ~250 mm/d), with delays at intervals of ~12 h at each synapse. Once the virus enters the CNS, it rapidly disseminates to other regions of the CNS via fast axonal transport along neuroanatomic connections. Neurons are prominently infected in rabies; infection of astrocytes is unusual. After CNS infection becomes established, there is centrifugal spread along sensory and autonomic nerves to other tissues, includ ing the salivary glands, heart, adrenal glands, and skin. Rabies virus replicates in acinar cells of the salivary glands and is secreted in the saliva of rabid animals that serve as vectors of the disease. There is no well-documented evidence for hematogenous spread of rabies virus. Pathologic studies show mild inflammatory changes in the CNS in rabies, with mononuclear inflammatory infiltration in the leptomen inges, perivascular regions, and parenchyma, including microglial nodules called Babes nodules. Degenerative neuronal changes usually are not prominent, and there is little evidence of neuronal death; neuronophagia is observed occasionally. The pathologic changes are surprisingly mild in light of the clinical severity and fatal outcome of the disease. The most characteristic pathologic finding in rabies is the Negri body (Fig. 214-4). Negri bodies are eosinophilic cytoplasmic inclusions in brain neurons that are composed of rabies virus pro teins and viral RNA. These inclusions occur in a minority of infected neurons, are commonly observed in Purkinje cells of the cerebellum

Brain

Centrifugal spread along nerves to salivary glands, skin, cornea, and other organs Eye Salivary glands

Virus binds to nicotinic acetylcholine receptors at neuromuscular junction

Replication in motor neurons of the spinal cord and local dorsal root ganglia and rapid ascent to brain Dorsal root ganglion Sensory nerves to skin Skeletal muscle

Virus travels within axons in peripheral nerves via retrograde fast axonal transport PART 5 Infectious Diseases Spinal cord Viral replication in muscle

Virus inoculated

FIGURE 214-3 Schematic representation of events in rabies pathogenesis following peripheral inoculation of rabies virus by an animal bite. (Reproduced with permission from AC Jackson: Pathogenesis, in Rabies: Scientific Basis of the Disease and Its Management, 3rd ed. Oxford, UK, Elsevier Academic Press, 2013.) and in pyramidal neurons of the hippocampus, and are less frequently seen in cortical and brainstem neurons. Negri bodies are not observed in all cases of rabies. The lack of prominent degenerative neuronal changes has led to the concept that neuronal dysfunction—rather than neuronal death—is responsible for clinical disease in rabies. Experimental studies indicate that oxidative stress due to mitochon drial dysfunction plays an important role. The basis for behavioral changes, including the aggressive behavior of rabid animals, is not well understood but may be related to infection of serotonergic neu rons in the brainstem. ■ ■CLINICAL MANIFESTATIONS For rabies prevention, the emphasis must be on postexposure prophy laxis (PEP) initiated after a recognized exposure and before any symp toms or signs develop. Rabies should usually be suspected on the basis of the clinical presentation with or without a history of an exposure. The disease generally presents as atypical encephalitis with relative preservation of consciousness. Rabies may be difficult to recognize late in the clinical course when progression to coma has occurred. A minority of patients (~20%) present with acute flaccid paralysis. There are prodromal, acute neurologic, and comatose phases that usually progress to death despite aggressive therapy (Table 214-1).

Prodromal Features The clinical features of rabies begin with nonspecific prodromal manifestations, including fever, malaise, head ache, nausea, and vomiting. Anxiety or agitation also may occur. The earliest specific neurologic symptoms of rabies include paresthesias, pain, or pruritus near the site of the exposure, one or more of which occur in 50–80% of patients and strongly suggest rabies. The wound has usually healed by this point, and these symptoms prob ably reflect infection with associated inflam matory changes in local dorsal root or cranial sensory ganglia.

Infection of brain neurons with neuronal dysfunction Encephalitic Rabies Two acute neuro logic forms of rabies are seen in humans: the encephalitic (furious) form in 80% and the paralytic form in 20%. Some of the manifesta tions of encephalitic rabies, including fever, confusion, hallucinations, combativeness, and seizures, may be seen in other viral encephaliti des as well. Autonomic dysfunction is common in rabies and may result in hypersalivation, gooseflesh, cardiac arrhythmia, and priapism. In encephalitic rabies, episodes of hyperexcitability are typically followed by periods of complete lucidity that become shorter as the disease progresses. Rabies encephalitis is distinguished by early brainstem involvement, which results in the classic features of hydrophobia (involun tary, painful contraction of the diaphragm and accessory respiratory, laryngeal, and pharyn geal muscles in response to swallowing liquids)

(Fig. 214-5) and aerophobia (the same features caused by stimulation from a draft of air). These symptoms are probably due to dysfunction of infected brainstem neurons that normally inhibit inspiratory neurons near the nucleus ambiguus, resulting in exaggerated defense reflexes that protect the respiratory tract. The combination of hypersalivation and pharyngeal dysfunction is

responsible for the classic appearance of “foaming at the mouth.” Brainstem dysfunction progresses rapidly, and coma—followed within days by death—is the rule unless the course is prolonged by supportive measures. With such measures, late complications can include cardiac and/or respiratory failure, disturbances of water balance (syndrome of inappropriate antidiuretic hormone secretion or diabetes insipidus), noncardiogenic pulmonary edema, and gastrointestinal hemorrhage. Cardiac arrhythmias may be due to dysfunction affecting vital centers in the brainstem or autonomic pathways or to myocarditis. Multipleorgan failure is common in patients treated aggressively in critical care units. Paralytic Rabies About 20% of patients have paralytic rabies in which muscle weakness predominates and cardinal features of encephalitic rabies (hyperexcitability, hydrophobia, and aerophobia) are lacking. There is early and prominent flaccid muscle weakness, often beginning in the bitten extremity and spreading to produce quadriparesis and facial weakness. Sphincter involvement is common, sensory involvement is usually mild, and these cases are commonly misdiagnosed as Guillain-Barré syndrome. Patients with paralytic rabies generally survive a few days longer than those with encephalitic rabies, but multiple-organ failure nevertheless ensues. ■ ■LABORATORY INVESTIGATIONS Most routine laboratory tests in rabies yield normal results or show nonspecific abnormalities. Complete blood counts are usually nor mal. Examination of cerebrospinal fluid (CSF) often reveals mild

FIGURE 214-4 Three large Negri bodies in the cytoplasm of a cerebellar Purkinje cell from an 8-year-old boy who died of rabies after being bitten by a rabid dog in Mexico. (Reproduced with permission from AC Jackson, E Lopez-Corella. N Engl J Med 335:568, 1996; © Massachusetts Medical Society.) mononuclear-cell pleocytosis with a mildly elevated protein level. Severe pleocytosis (>1000 white cells/μL) is unusual and should prompt a search for an alternative diagnosis. Imaging is usually per formed to exclude other diagnostic possibilities. Computed tomogra phy (CT) head scans are usually normal in rabies. Magnetic resonance imaging (MRI) brain scans may show signal abnormalities in the brain stem or other gray-matter areas, but these findings are variable and nonspecific. Electroencephalograms typically show only nonspecific abnormalities. Of course, important tests in suspected cases of rabies include those that may identify an alternative, potentially treatable diagnosis (see “Differential Diagnosis,” below). ■ ■DIAGNOSIS In North America, a diagnosis of rabies often is not considered until relatively late in the clinical course, even with a typical clinical pre sentation. This diagnosis should be considered in patients presenting with acute atypical encephalitis or acute flaccid paralysis, including those in whom Guillain-Barré syndrome is suspected. The absence of an animal-bite history is common in North America, particularly due to unrecognized bat exposures. The lack of hydrophobia is not unusual in rabies. Once rabies is suspected, rabies-specific laboratory tests should be performed to confirm the diagnosis. Diagnostically TABLE 214-1 Clinical Stages of Rabies STAGE TYPICAL DURATION SYMPTOMS AND SIGNS Incubation period 20–90 days None Prodrome 2–10 days Fever, malaise, anorexia, nausea, vomiting; paresthesias, pain, or pruritus at the wound site Acute Neurologic Disease Encephalitic (80%) 2–7 days Anxiety, agitation, hyperactivity, bizarre behavior, hallucinations, autonomic dysfunction, hydrophobia Paralytic (20%) 2–10 days Flaccid paralysis in limb(s) progressing to quadriparesis with facial paralysis Coma, deatha 0–14 days aRecovery is rare. Source: Adapted from MAW Hattwick: Rabies virus, in Principles and Practice of Infectious Diseases, GL Mandell et al (eds). New York, Wiley, 1979.

FIGURE 214-5 Hydrophobic spasm of inspiratory muscles associated with terror in a patient with encephalitic (furious) rabies who is attempting to swallow water. (Copyright DA Warrell, Oxford, UK;

with permission.) CHAPTER 214 useful specimens include serum, CSF, fresh saliva, skin biopsy samples from the neck, and brain tissue (rarely obtained before death). Because skin biopsy relies on the demonstration of rabies virus antigen and/or RNA in cutaneous nerves at the base of hair follicles, samples are usu ally taken from hairy skin at the nape of the neck. Corneal impression smears are of low diagnostic yield and are generally not performed. Negative antemortem rabies-specific laboratory tests never exclude a diagnosis of rabies, and tests may need to be repeated after an interval for diagnostic confirmation. Rabies Virus–Specific Antibodies In a previously unimmu nized patient, serum neutralizing antibodies to rabies virus are diagnostic. However, because rabies virus infects immunologically privileged neuronal tissues, serum antibodies may not develop until late in the disease. Antibodies may be detected within a few days after the onset of symptoms, but some patients die without detectable anti bodies. The presence of rabies virus–specific neutralizing antibodies in the CSF suggests rabies encephalitis, regardless of immunization status. A diagnosis of rabies is questionable in patients who recover from their illness without developing serum neutralizing antibodies to rabies virus. RT-PCR Amplification Detection of rabies virus RNA by RTPCR is highly sensitive and specific. This technique can detect virus in fresh saliva samples, skin biopsy specimens, CSF (less sensitive), and brain tissues. In addition, RT-PCR with genetic sequencing can distinguish among rabies virus variants, permitting identification of the probable source of an infection. Direct Fluorescent Antibody Testing Direct fluorescent anti body (DFA) testing with rabies virus antibodies conjugated to fluo rescent dyes is highly sensitive and specific for the detection of rabies virus antigen in tissues; the test can be performed quickly and applied to skin biopsy and brain tissue samples. In skin biopsy samples, rabies virus antigen may be detected in cutaneous nerves at the base of hair follicles. Rabies and Other Rhabdovirus Infections ■ ■DIFFERENTIAL DIAGNOSIS The diagnosis of rabies may be difficult without a history of animal exposure, and no exposure to an animal (e.g., a bat) may be recalled. The presentation of rabies is usually quite different from that of acute

viral encephalitis due to most other causes, including herpes simplex encephalitis and arboviral (e.g., West Nile) encephalitis. Early neuro logic symptoms may occur at the site of the bite, and there may be early features of brainstem involvement with preservation of consciousness. Anti–N-methyl-d-aspartate receptor (anti-NMDA) encephalitis occurs in young patients (especially females) and is characterized by behav ioral changes, autonomic instability, hypoventilation, and seizures. Many other antibodies are also associated with autoimmune encepha litis. Postinfectious (immune-mediated) encephalomyelitis may follow influenza, measles, mumps, and other infections; it may also occur as a sequela of immunization with rabies vaccines derived from neural tissues, which are now infrequently used and only in resource-limited and resource-poor countries. Rabies may present with unusual neuro psychiatric symptoms and may be misdiagnosed as a psychiatric dis order. Rabies hysteria (now classified as a somatic symptom disorder) may occur as a psychological response to the fear of rabies and is often characterized by a shorter incubation period than rabies, aggressive behavior, inability to communicate, and a long course with recovery.

As previously mentioned, paralytic rabies may mimic GuillainBarré syndrome. In these cases, fever, bladder dysfunction, a normal sensory examination, and CSF pleocytosis favor a diagnosis of rabies. Conversely, Guillain-Barré syndrome may occur as a complication of rabies vaccination with a neural tissue–derived product (e.g., suckling mouse brain vaccine) and may be mistaken for paralytic rabies (i.e., vaccine failure). TREATMENT Rabies PART 5 Infectious Diseases There is no established treatment for rabies. Aggressive manage ment with supportive care in critical care

units has resulted in the survival of at least 33 patients with rabies. Many of these survivors have recently been reported from India. There have been many recent treatment failures (>60) with the combination of therapeutic (induced) coma, antiviral drugs, and sometimes ketamine— measures that were used in a healthy survivor in whom neutralizing antibodies to rabies virus were detected at presentation. No antiviral therapy has demonstrated any efficacy in the treatment of rabies. Expert opinion is recommended before a course of experimental therapy is embarked upon. A palliative approach may be appropri ate for many patients who are not considered candidates for aggres sive management. ■ ■PROGNOSIS Rabies is an almost uniformly fatal disease but is nearly always prevent able after recognized exposures with appropriate postexposure therapy during the early incubation period (see below). All but 2 of 33 docu mented survivors of rabies received one or more doses of rabies vaccine before disease onset. The survivors who had not received vaccine had neutralizing antibodies to rabies virus in CSF at clinical presentation. Most patients with rabies die within several days of the onset of illness, despite aggressive care in a critical care unit. ■ ■PREVENTION Postexposure Prophylaxis Since there is no effective therapy for rabies, it is extremely important to prevent the disease after an animal exposure. Figure 214-6 shows the steps involved in making decisions about PEP. Based on the exposure history and local epidemiologic information, the physician must decide whether initiation of PEP is warranted. Healthy dogs, cats, or ferrets may be confined and observed for 10 days. PEP is not necessary if the animal remains healthy. If the animal develops signs of rabies during the observation period, it should be euthanized immediately; the head should be transported to the laboratory under refrigeration, rabies virus should be sought by DFA testing, and viral isolation should be attempted by cell culture and/or mouse inoculation. Any animal other than a dog, cat, or ferret should be euthanized immediately and the head submitted for laboratory

Rabies prophylaxis Did the animal bite the patient or did saliva contaminate a scratch, abrasion, open wound, or mucous membrane? No None Yes Is rabies known or suspected to be present in the species and the geographic area? None No Yes No Was the animal captured? RIG and vaccine Yes Yes Was the animal a normally behaving dog, cat, or ferret? Does the animal become ill under observation over the next 10 days? Yes No No Does laboratory examination of the brain by fluorescent antibody staining confirm rabies? No None Yes RIG and vaccine FIGURE 214-6 Algorithm for rabies postexposure prophylaxis. RIG, rabies immune globulin. (From L Corey, in Harrison’s Principles of Internal Medicine, 15th ed. E Braunwald et al [eds]: New York, McGraw-Hill, 2001.) examination. In high-risk exposures and in areas where canine rabies is endemic, rabies prophylaxis should be initiated without waiting for laboratory results. If the laboratory results prove to be negative, it may safely be concluded that the animal’s saliva did not contain rabies virus, and immunization should be discontinued. If an animal escapes after an exposure, it must be considered rabid, and PEP must be initiated unless information from public health officials indicates otherwise (i.e., there is no endemic rabies in the area). Although controversial, the use of PEP may be warranted when a person (e.g., a small child or a sleeping adult) has been present in the same space as a bat and an unrecognized bite cannot be reliably excluded. PEP includes local wound care and both active and passive immuni zation. It is important that current recommendations are followed very closely because minor deviations can lead to failure of prophylactic measures. Local wound care is essential and may greatly decrease the risk of rabies virus infection. Wound care should not be delayed, even if the initiation of immunization is postponed pending the results of the 10-day observation period. All bite wounds and scratches should be washed thoroughly with soap and water. Devitalized tissues should be debrided, tetanus prophylaxis given, and antibiotic treatment initiated whenever indicated. Previously unvaccinated persons (but not those who have

previ ously been immunized) should be passively immunized with rabies immune globulin (RIG). If RIG is not immediately available, it should be administered no later than 7 days after the first vaccine dose. After day 7, endogenous antibodies are being produced, and passive immu nization may actually be counterproductive. If anatomically feasible, the entire dose of RIG (20 IU/kg) should be infiltrated at the site of the bite, and any RIG remaining after infiltration of the bite site should be administered IM at a distant site. Recent recommendations by the World Health Organization indicate that under certain circumstances the remainder of the dose does not need to be administered after local

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