Rabies

Rare Human Infection – Common Questions

Rodney E. Willoughby Jr, MD

KEYWORDS

• Rabies • Lyssavirus • Encephalitis • Diagnosis • Therapy • Mortality
• Brain diseases • Biopterin

KEY POINTS

- Rabies may cause a continuum of disease severity and is treatable.
- Modern pre-exposure prophylaxis and postexposure prophylaxis (PEP) is highly effective.
- Rabies behaves like and is treated as an acquired metabolic disorder.

Rabies is an acute and rapidly progressive encephalitis that is almost always fatal. It is a syndrome caused by 12 lyssavirus species, including rabies virus (genotype 1 lyssavirus). Rabies is a global zoonosis – only the continent of Antarctica is rabies-free. Rabies virus is the only lyssavirus present in the Americas. Many so-called rabies-free countries contain other lyssaviruses in wildlife, but the intersection of the reservoir species for these lyssaviruses with humans is rare.

NATURAL HISTORY

Lyssaviruses are negative-sense, single-stranded, enveloped RNA viruses that contain a single-surface glycoprotein and a ribonucleoprotein core. Rabies virus is transmitted by saliva or infected neural tissue. It is rapidly inactivated by desiccation and sunlight. Infection requires contamination of infected saliva or neural tissue into a bite wound or broken skin or onto mucosa. Natural transmission by aerosol is debated. Ingestion requires large doses for infection. There is no hematogenous or congenital transmission. Blood, urine, and feces are not infectious in animals or humans. There have been 4 outbreaks of rabies associated with solid organ transplantation and 13 by corneal implantation. Rabies virus is considered a potential biological weapon.

The author has nothing to disclose.
Pediatric Infectious Diseases, Children's Hospital of Wisconsin, C450, PO Box 1997, Milwaukee, WI 53201-1997, USA
E-mail address: rewillou@mcw.edu

Infect Dis Clin N Am 29 (2015) 637–650
http://dx.doi.org/10.1016/j.idc.2015.07.006 **id.theclinics.com**

Rabies virus replicates poorly and at low levels in local tissues, including muscle (dog rabies) and skin (bat rabies). Inefficient virus replication avoids immune detection and results in highly variable and often prolonged incubation periods (up to 7 years).[1] There is no known mechanism for latent infection by rabies virus, although the incubation period is prolonged during hibernation. Louis Pasteur capitalized on the long incubation period of rabies to develop highly effective PEP. Rabies virus is highly neurotropic, replicating rapidly once it enters neurons. Because the nervous system is a privileged immunologic site, rabies virus continues to evade the adaptive immune response for many days after entering the central nervous system (CNS). Motor fibers transmit rabies virus efficiently by rapid retrograde axonal transport and it is disseminated exclusively across synapses, at the rate of approximtely 1 synaptic network every 12 hours. Dorsal root ganglia are also infected by rabies virus and contribute to the clinical syndrome but do not extend the infection.[2] Synaptic transmission within the brain and spinal cord to autonomic nerves results in prominent clinical signs that lag behind motor and sensory findings.[2]

The mechanism of death from rabies remains unclear. The virus is poorly cytopathic and poorly immunogenic, so anatomic damage is minimal. Behavioral effects are initially subtle and remain intermittent until the patient lapses into coma within a week of hospitalization. In animal models, there are several days during which the CNS is massively infected, yet there are no symptoms or signs. Once in the CNS, the virus engages in centrifugal spread, involving all peripheral nerves. The peripheral spread to the salivary glands and the subtle, intermittent behavioral changes facilitate transmission to the next host. Dysautonomia, sensory denervation, and paralysis ensue. Humans and most small rodents and lagomorphs are dead-end hosts. There has never been a proven case of human-to-human transmission of rabies through clinical care or at autopsy, other than by solid organ or corneal transplantation.[3]

The clinical prodrome is vague, variable in duration (3–10 days) and flulike, often with sore throat and sleep disturbance. This is followed by episodic changes in alertness, agitation, aggression, panic, and hallucinations. Characteristic features that assist in distinguishing rabies from other forms of encephalitis and encephalopathy are listed in **Box 1**. Although classic teaching differentiates “furious” (encephalitic) and “dumb” (paralytic) rabies, in my experience there tends to be a continuum of signs and symptoms. Paresis occurs in both. A case report and a dog model suggest that

Box 1
Distinguishing characteristics of rabies encephalitis

1. Episodes of altered arousal, behavior, cognition, and dysautonomia interspersed with complete normalcy
2. Pain, pruritus, and dysesthesias referable to the bitten limb
3. Myoclonic jerks, paresis referable to the bitten limb
4. Dysphagia, hydrophobia, and aerophobia
5. Dysautonomia, including catecholamine surges, bradyarrhythmias, hypersalivation, piloerection, sweating, and priapism.
6. Guillain-Barré–like syndromes that include urinary and fecal retention or other dysautonomia
7. Orofacial dyskinesias and myokymia
8. History of exposure (foreign travel, immigration, attic remodeling, cabin ownership, hunting or dressing the game, spelunking, wildlife rehabilitation or organ transplantation)