



# RABIES

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### INTRODUCTION

Rabies is a lethal zoonotic disease responsible for the deaths of 60,000 people annually.<sup>1,2</sup> Rabies virus (RABV) is a lyssavirus prototype with a mortality rate of nearly 100% after symptom onset.<sup>1,3-4</sup> Following an incubation period of 1-3 months after exposure, hosts develop encephalitis leading to two possible symptomatologies. A clinical presentation of RABV is encephalitic rabies, characterised by hydrophobia, agitation, and hypersalivation. Alternatively, RABV may also present as paralytic rabies, characterised by muscle weakness and paralysis. Both types eventually result in a comatose state followed by death.<sup>2,3</sup> Despite mass vaccination campaigns in developing nations aiming to reduce infection across mammalian populations, the virus continues to gain prevalence in novel species and geographic areas, proving to be a threat of increasing magnitude.<sup>1</sup>

### DIAGNOSIS & TRANSMISSION

RABV is a mammalian-borne disease, with dog bites contributing to 99% of all rabies cases in humans. Minor exposures caused by superficial lesions are more likely to be unrecognised and subsequently unreported.<sup>1,3</sup> RABV transmission occurs most commonly through contact between the saliva of an infected animal, and the mucosal membrane, or impaired skin barrier, of the recipient.<sup>1</sup> RABV can infect most cell types, and there are many mechanistic differences leading to infection in humans.

This results in varied pathogenesis and clinical presentation.<sup>1</sup> The incubation period of RABV is variable, but typically lies within 20-90 days, during which the host is asymptomatic due to a lack of immune response. Once symptoms arise in later stages of the disease, the viral load is intractably high and more difficult to combat.<sup>1,4</sup> Thus, rapid diagnosis is essential for maximising patient outcomes. This is often done using magnetic resonance imaging to detect lesions and swelling in the brain, in addition to standardised laboratory tests to detect RABV and its antibodies.<sup>4</sup> When using fluorescence antibody testing in RABV infection diagnosis, it is important to use multiple sample sources, such as tears, hair follicles, saliva, and urine, for the highest possible likelihood of disease identification.<sup>5</sup>

### MECHANISM

In hosts, RABV generally infects peripheral nerves at the motor end plate of neuromuscular junctions, and may also infect muscle cells. RABV binds to nicotinic acetylcholine neuronal receptors via its glycoprotein, the viral determinant of RABV infection.<sup>6</sup> After receptor-mediated endocytosis, RABV is packaged in endosomal transport vesicles and retrogradely transported along axons.<sup>6</sup> In the neuronal cell body, RABV releases viral RNA polymerase and a strand of viral RNA in the cytoplasm, containing the N, P, M, G and L genes, encoding nucleoprotein, phosphoprotein, matrix protein, glycoprotein, and large RNA polymerase protein, respectively.<sup>6-8</sup> The accumulation of viral proteins leads to the formation of cytoplasmic inclusion bodies, which are the site of viral RNA synthesis.<sup>6,9</sup> During replication, full-length, positive-stranded RNA is replicated from the viral genomic RNA, acting as a template for progeny negative-stranded RNA production.<sup>9</sup> During the assembly process, the nucleoprotein, phosphoprotein and large polymerase proteins form a helical ribonucleoprotein (RNP) complex, while encapsulating the negative-stranded genomic RNA.<sup>8,9</sup> The matrix protein forms a capsule around the RNP complex before migrating to the postsynaptic neuronal membrane to bind the glycoproteins.<sup>8,9</sup> Newly synthesized RABVs are then transmitted to neighbouring presynaptic neurons in a viral glycoprotein-dependent manner, initiating the cycle once again.<sup>6</sup>

RABV primarily uses motor pathways to the spinal cord, disseminating throughout the central nervous system (CNS).<sup>10</sup>

Initial symptoms of encephalitic RABV may include fever, malaise, cough, pain, paresthesia, or pruritus at the bite site.

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Subsequently, patients develop hydrophobia, hypersalivation, lacrimation, and pupil dilation, all of which are signs of autonomic dysfunction and indicate that the infection has spread to the brain.<sup>11</sup> Encephalitic RABV mainly involves extensive neuronal damage and inflammation to the brain stem, cerebrum, and limbic system, leading to increased aggression and other behavioural changes.<sup>12</sup> In contrast, paralytic RABV is categorized by flaccid muscle weakness, particularly in the laryngeal muscle.<sup>10</sup> The spread of RABV to the CNS leads to a condition called 'bulbar paralysis', which involves the dysfunction of muscles innervated by the glossopharyngeal, vagus, and hypoglossal nerves. These nerves innervate various muscles in the throat, including the laryngeal muscle, thus leading to difficulty in swallowing, voice changes, and eventually, respiratory failure with virus progression. The pathogenesis of paralytic RABV is poorly understood, but it often causes extensive neuronal damage to the medulla and the spinal cord.<sup>12</sup> The absence of a significant immune response to the infection and diminished number of peripheral B lymphocytes may be correlated with the appearance of paralytic RABV. After the dissemination of RABV in the CNS, it will then spread to peripheral non-nervous tissues, like the salivary glands, allowing for transmission of the virus to its next host.<sup>11</sup>

### TREATMENT

After symptom onset, rabies is almost always fatal. However, this can be prevented through vaccination before or following exposure.<sup>2</sup> The intradermal rabies vaccine is highly effective in preventing infection when coupled with routine wound management, even following exposure to a severe dog bite. The administration of rabies immunoglobulins may also be recommended to neutralise RABV at the inoculation site for patients who experienced a high-risk exposure.<sup>2</sup> Pre-exposure prophylaxis is also recommended for certain at-risk populations, such as those working in veterinary settings, laboratories, and other high-incidence settings.<sup>2</sup> The Milwaukee Protocol was the standard treatment protocol for RABV infection from 2004 to 2015, but is no longer recommended.<sup>13,14</sup> However, this treatment plan is still used despite controversies surrounding its risks.<sup>13,14</sup> The Milwaukee Protocol involves inducing a comatose state and administering high doses of antivirals and sedatives such as ketamine and barbiturates.<sup>13</sup> It was later updated to advise against coma induction after repeated adverse patient outcomes, and introduced the use of benzodiazepines in conjunction with ketamine usage to minimise suffering and autonomic nervous system dysfunction.<sup>13</sup> As the onset of clinical symptoms is a likely predictor of eventual death, it is imperative to reassess the best course of action for surveillance and preventive measures worldwide.<sup>1,2</sup>

1. Fisher CR, Streicker DG, Schnell MJ. The spread and evolution of rabies virus: Conquering new frontiers. *Nat Rev Microbiol.* 2018;16(4):241–55. Available from: doi:10.1038/nrmicro.2018.11.
2. World Health Organization. *Frequently asked questions about rabies for Clinicians.* Geneva (Switzerland): World Health Organization, 2018. 18 p. Report No.: 3.
3. Fooks AR, Cliquet F, Finke S, Freuling C, Hemachudha T, Mani RS, et al. Rabies. *Nat Rev Dis Primers.* 2017;3(1):17091. Available from: doi:10.1038/nrdp.2017.91.
4. Hemachudha T, Ugolini G, Wacharapluessadee S, Sungkarat W, Shuangshoti S, Laothamatas J. Human rabies: Neuropathogenesis, diagnosis, and management. *Lancet Neurol.* 2013;12(5):498–513. Available from: doi:10.1016/S1474-4422(13)70038-3.
5. Hemachudha T, Wacharapluessadee S. Antemortem Diagnosis of Human Rabies. *Clin Infect Dis.* 2004;39(7):1085–86. Available from: doi:10.4103/0972-2327.40219.
6. Fooks AR, Cliquet F, Finke S, Freuling C, Hemachudha T, Mani RS, et al. Rabies. *Nat Rev Dis Primers.* 2017;3(1):1–19. Available from: doi:10.1038/nrdp.2017.91.
7. Li S, Pan Y, Teng H, Shan Y, Yang G, Wang H. Revealing the cell entry dynamic mechanism of single rabies virus particle. *Chem Res Chinese Universities.* 2022;38(3):838–842. Available from: doi:10.1007/s40242-022-2069-y.
8. Masatani T, Ito N, Shimizu K, Ito Y, Nakagawa K, Sawaki Y, et al. Rabies virus nucleoprotein functions to evade activation of the RIG-I-mediated antiviral response. *J Virol.* 2010;84(8):4002–12. Available from: doi:10.1128/JVI.02220-09.
9. Rupprecht CE. *Medical Microbiology.* 4th ed. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 61.
10. Jackson AC. Update on rabies. *Res Rep Trop Med.* 2011;2:31–43. Available from: doi:10.2147/RRTM.S16013.
11. Jackson AC, Wunner WH. *Rabies: Scientific Basis of the Disease and Its Management.* 2nd ed. San Diego: Elsevier Science & Technology; 2007. 309–351 p.
12. Awasthi M, Parmar H, Patankar T, Castillo M. Imaging findings in rabies encephalitis. *AJNR Am J Neuroradiol.* 2001;22(4):677–80.
13. Singh R, Singh KP, Cherian S, Saminathan M, Kapoor S, Manjunatha Reddy GB, et al. Rabies – epidemiology, pathogenesis, public health concerns and advances in diagnosis and control: A comprehensive review. *Vet Q.* 2017;37(1):212–51. Available from: doi:10.1080/01652176.2017.1343516.
14. Arslan F, Vajaboglu H. An update to the critical appraisal of Milwaukee protocol. *World J Surg.* 2023;6:1471. Available from: doi:10.1101/2022.12.14.22283490.