COMMENTARY

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Rabies: A Timeless Zoonotic Threat

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Rabies is among the earliest zoonotic diseases documented in human history. Despite centuries of scientific progress, it remains one of the most feared infectious diseases because of its severe and rapidly progressive neurological manifestations and its nearly 100% case fatality rate once clinical symptoms develop. The history of rabies closely parallels the development of modern medicine, from mystical beliefs and traditional remedies to microbiology, immunology, vaccination, and contemporary global public health. Rabies has been documented for nearly 4000 years. Early descriptions appear in Mesopotamian tablets and ancient Egyptian records. In ancient Greece, Hippocratic writings described manifestations consistent with hydrophobia, Aristotle recognized transmission from rabid dogs to humans and other animals, and Galen associated transmission with saliva and advocated cauterization of bite wounds. During the Middle Ages, physicians including Rhazes, Avicenna, and others recorded observations on rabies and animal bites. For centuries, however, treatment was dominated by cauterization, magical incantations, religious rituals, and other traditional remedies because the infectious cause of the disease was unknown (1). The nineteenth century marked a major turning point. Advances in experimental medicine established the infectious nature of rabies and its strong neurotropic character. Louis Pasteur's studies led to the development of the first effective rabies vaccine and its successful use for post-exposure prophylaxis (PEP) in Joseph Meister in 1885, a landmark achievement in the history of preventive medicine (2). During the twentieth century, advances in virology, immunology, neuropathology, and epidemiology substantially expanded our understanding of rabies.

The classical causative agent of rabies is *Rabies lyssavirus*. Although uncommon, human infections have also been reported with other members of the genus *Lyssavirus*. To date,

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three major phylogenetic groups of lyssaviruses have been described. Current rabies vaccines and rabies immunoglobulins (RIGs) provide effective protection against members of phylogenetic group 1, but their effectiveness against viruses belonging to other phylogenetic groups is more limited. Lyssaviruses have been detected on every continent except Antarctica, and bats serve as the natural reservoirs for approximately 80–90% of recognized lyssavirus species (3,4). Bats are therefore considered important natural reservoirs not only for classical rabies virus but also for lyssaviruses with the potential to emerge as human pathogens in the future.

Despite being almost entirely preventable, rabies remains a significant cause of mortality worldwide. The global epidemiology of human rabies is closely linked to the circulation of the virus among animal reservoirs. Rabies is estimated to cause approximately 59,000 human deaths each year in more than 150 countries, with around 95% of these deaths occurring in Africa and Asia. In endemic regions, dog-mediated transmission remains the predominant route of human infection, accounting for approximately 99% of human rabies cases. Children under the age of 15 bear a disproportionate share of this burden, representing nearly 40% of fatalities. Because rabies is frequently underdiagnosed and underreported, the true global burden is likely to be substantially higher. Human rabies acquired from bats is relatively uncommon but is well documented. Hundreds of molecularly confirmed cases have been reported in Latin America, along with dozens of cases in North America (5). In Australia, four fatal human infections caused by Australian bat lyssavirus have been reported (6). Rabies virus is transmitted primarily through bites or scratches or through contact between the saliva of infected animals and broken skin or mucous membranes. Human-to-human transmission of rabies has not been documented through routine person-to-person contact. However, transmission through organ transplantation from infected donors with undiagnosed rabies has been documented in several cases (7).

Clinically, rabies is generally classified into two major forms: encephalitic rabies, characterized by prominent agitation and neurological hyperexcitability, and less common paralytic rabies, which presents predominantly with progressive flaccid paralysis and is less frequently observed. Both forms are rapidly progressive and are almost invariably fatal once clinical symptoms develop. Diagnosing rabies requires a comprehensive assessment of clinical presentation, exposure history, epidemiological context, and laboratory findings. Because rabies progresses rapidly once clinical symptoms develop, early clinical suspicion is critical. Paresthesia, pain, or unusual sensations at the site of a previous bite or exposure are particularly suggestive of rabies. Rabies should be included in the differential diagnosis of patients with unexplained acute encephalitis or a Guillain-Barré syndrome-like paralytic illness, particularly when there is a relevant history of animal exposure, including bat exposure, residence in, or travel to a rabies-endemic area (8). Laboratory confirmation in living patients requires examining multiple clinical specimens because no single test reliably excludes rabies. Recommended specimens include saliva, cerebrospinal fluid, serum, and a skin biopsy obtained from the nape of the neck, just above the hairline, which contains cutaneous nerves and can provide evidence of viral infection. Several diagnostic methods may be employed. These include detecting rabies virus antigen in skin biopsy specimens by direct immunofluorescence, detecting rabies virus-specific antibodies in serum and cerebrospinal fluid (CSF), and detecting viral RNA by reverse transcription-polymerase chain reaction (RT-PCR) in saliva, CSF, or skin biopsy specimens (9). Because viral shedding may be intermittent and test sensitivity varies among specimen types, testing multiple specimens with different methods is recommended when rabies is suspected.

Currently, no proven effective treatment exists once clinical symptoms have developed. For many years, clinical rabies was considered uniformly fatal. The Milwaukee Protocol, an experimental treatment strategy, was initially used in a 15-year-old girl who developed rabies following a bat bite. She survived, although she was left with persistent mild neurological sequelae (10). The protocol was based primarily on the induction of a therapeutic coma using benzodiazepines and barbiturates, combined with

antiviral therapy including ketamine, ribavirin, and amantadine. Approximately 34 cases of survival following clinical rabies have been described in the literature. Common features among reported survivors include early development of high levels of neutralizing antibodies, intensive supportive care, and, in some cases, vaccination before the onset of clinical symptoms. Most survivors have been left with neurological sequelae of varying severity. Importantly, the diagnosis was not unequivocal in several reported cases, and none of the patients had received PEP according to recommended protocols. Subsequent experience with the Milwaukee Protocol has not demonstrated a consistent clinical benefit, and its routine use is therefore not supported by current evidence (11). Experimental treatment research is exploring antiviral compounds, immunomodulatory strategies, and monoclonal antibodies (mAbs) with the potential to access the central nervous system, including intrathecal delivery (12). The pathophysiological mechanisms responsible for rabies-associated neuronal dysfunction and neurological injury remain incompletely characterized. A better understanding of viral neuroinvasion, neuronal responses, and host-virus interactions is essential for identifying new therapeutic targets and accelerating the development of effective treatments for symptomatic rabies.

The development of cell-culture-based vaccines gradually replaced less safe nerve-tissue vaccines, providing a safer and more effective means of rabies prevention. Pre-exposure prophylaxis is recommended for individuals who have frequent or occupational exposure to animals at risk for rabies, whereas PEP should be administered to individuals who have had a potential rabies exposure, according to a risk assessment and applicable guidelines. Immediate wound washing with soap and water for at least 15 minutes, active immunization with a modern cell-culture rabies vaccine administered on a multidose schedule, and, for higher-risk exposures, passive immunization with RIG around the wound is nearly 100% effective in preventing rabies (13). Nevertheless, rare cases of rabies have been reported following apparently adequate PEP. These cases have most commonly been associated with errors in PEP administration, including inadequate wound cleansing, delayed initiation of PEP, insufficient RIG dosing, failure to infiltrate RIG into and around the wound, administration of vaccine into the gluteal region, failure to complete the recommended vaccination schedule, and the use of substandard or improperly handled vaccine products. True failure despite appropriately administered PEP is exceedingly rare (14). Failure of PEP despite correct and complete administration is exceptionally uncommon.

Despite the availability of safe and highly effective rabies vaccines, limited access to PEP remains a major challenge in global rabies control. One of the most significant advances in recent years has been the introduction of rabies virus-specific mAbs as an alternative to polyclonal RIG for passive immunization (15). Recombinant mAbs are a promising approach for improving the availability, quality, and reliability of passive immunization, particularly in settings where conventional RIG is difficult to procure. Adapting messenger RNA (mRNA) technology for rabies vaccine production offers many potential advantages, including rapid manufacturing, flexible antigen design, and the capacity for scalable production (16). Nevertheless, rabies mRNA vaccines remain investigational, and further preclinical and clinical studies are required to establish their safety.

Rabies control in humans cannot be achieved through human immunization alone. An effective, sustainable strategy requires a multifaceted approach that combines interrupting transmission at its animal source, vaccinating individuals and populations at increased risk, promptly and appropriately managing human exposures, community education, and effective surveillance and reporting. Because dogs are responsible for approximately 99% of human rabies cases, interrupting transmission within dog populations remains the cornerstone of rabies control, but culling dogs alone is neither effective nor sustainable for rabies prevention. September 28 marks the anniversary of the death of Louis Pasteur. This day provides an important opportunity to raise global awareness of rabies, reinforce the need for sustained efforts toward global elimination, and highlight the importance of a coordinated One Health approach that integrates human health, veterinary medicine, and public health.

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