

Current Status of Canine Rabies in China*

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Abstract

The number of human rabies cases acquired from dog bites constitutes a high proportion of the total rabies cases in China, although the number of human rabies cases has gradually decreased in recent years. The pivotal role of dogs in the spread of rabies indicates that controlling and preventing canine rabies could be a key step in eradicating human rabies in China. The primary aims of this review are to discuss the properties and pathogenesis of the rabies virus, the clinical signs and diagnosis of canine rabies, threshold host density and vaccination of dogs, and the prevention and control of canine rabies in China.

Key words: Canine rabies; Rabies virus; Vaccination; Prevention

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INTRODUCTION

Rabies is an ancient disease, but is still feared as one of the most fatal zoonotic diseases of humans and animals. The virus is transmitted to humans by direct contact with wild animals or indirectly through domestic animals exposed to infected wildlife. Once symptoms of the disease develop, the mortality rate is almost 100%. The first description of rabies may have been reported in the Old World before 2300 BC^[1]. Human rabies in China was first described around 556 BC in Master Zuo's "Commentary on Spring and Autumn Annals," and has persisted for more than 2500 years^[2]. Since 1950, the second year after the establishment of the People's Republic of China, human rabies has been listed in the Chinese National Statutory Notifiable Communicable Diseases (Group B)^[3]. Rabies is widely distributed around the globe.

Worldwide, over 55 000 people die of rabies each year, and about 95% of human deaths occur in Asia and Africa^[4]. From 1950 to 2010, an average of 2 037 cases per year were reported in China^[5].

The rabies virus (RABV) is responsible for human and animal rabies. The virus can infect animals and subsequently be spread to humans through the bite or scratch of an infected animal. All species of mammals are susceptible to rabies virus infection, and many wildlife species are natural reservoirs of the rabies virus. Cattle, pigs, sheep, fox, sika deer and rats have all been known, on rare occasions, to act as a source of rabies virus for humans^[6-8]. These mammals were reported to be mainly infected by rabid dogs. Therefore, dogs are the main carriers of rabies and are responsible for most of the human rabies deaths in China^[9]. The proportion of human rabies cases with a history of exposure to dogs in three Chinese provinces experiencing severe

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epidemics was 98% (Hunan), 96% (Guangxi), and 89% (Guangdong)^[10]. The current status and prevention of canine rabies in China will be discussed in this review.

Properties and Pathogenesis of Rabies Virus

The rabies virus is a member of the *Rhabdoviridae* family, which contains more than 175 viruses of vertebrates, invertebrates and plants. According to virion structure and serological relationships, four animal virus genera have been recognized in the *Rhabdoviridae* family. The rabies virus belongs to the genus *Lyssavirus*, together with other lyssaviruses including the European bat lyssaviruses 1 and 2. The bullet-shaped rabies virion contains a single negative-strand 11-15 Kb RNA genome. Generally, five proteins are present in mature rabies virus particles: nucleoprotein, phosphoprotein, matrix protein, glycoprotein, and RNA-dependent RNA polymerase. The glycoprotein plays an important role in pathogenicity and viral neurotropism because it carries neutralizing epitopes that are the targets of vaccine-induced immunity^[11-13]. The nucleoprotein has been used extensively for genetic typing and evolutionary studies because it is relatively conserved among reservoir-associated variants and geographic lineages^[14-15]. Rabies viruses can persist in the environment, especially under conditions where the pH \geq 7, but they are thermolabile and sensitive to ultraviolet irradiation. In clinical practice, detergent-based disinfectant is used to inactivate rabies viruses.

Rabies virus entry into host cells occurs through the fusion of viral envelope glycoproteins and receptors on the cell membrane, and all replication steps occur in the cytoplasm. Rabies virions are assembled by budding of nucleocapsids through the intracytoplasmic membranes of infected neurons and through plasma membranes in salivary gland epithelial cells. The replication process is slow and does not cause cytopathic effect, but it produces prominent cytoplasmic inclusion bodies (Negri bodies) in infectious cells. Infection with rabies virus also causes minor morphologic changes in neurons, which may result in neurophysiologic dysfunction. Viral persistence is generally life-long in infected hosts.

The rabies virus can be transmitted to humans or other animals through a bite or scratch in the skin or mucous membranes. Rabid animals are not viremic and their blood is not infectious. The average

incubation period in dogs is approximately two months, but may vary from two weeks to several months depending on the breed and the transmitted virus dose. The virus replicates in striated muscle and connective tissue at the site of inoculation, and enters the peripheral nerves through the neuromuscular junction^[16]. Alternatively, it can infect peripheral nerves directly. Regardless of the manner of infection, viruses enter the central nervous system through the axonal route. The virus then travels via retrograde axonal transport to reach the salivary glands. At this point the animals become infectious, usually several days before clinical signs appear. The rabies virus can be widely disseminated throughout the organs.

Clinical Signs and Diagnosis of Canine Rabies

Any unexplained aggressive behavior or sudden behavior change in dogs should raise a suspicion of rabies. Rabies should be suspected when there has been a recent history of exposure to another rabid dog, as well as recent contact with wildlife or other suspicious animals. Most of the clinical signs are related to central and peripheral nervous system dysfunction due to abnormalities in neurotransmission rather than neuronal destruction. Two forms of rabies disease have been identified in dogs: furious and paralytic. The furious form has three clinical phases: prodromal, mad or psychotic, and paralytic. The prodromal period usually persists for one or two days, with symptoms of depression, photophobia, unresponsiveness, abnormal appetite, dysphagia, and mydriasis. The prodromal period is followed by a mad or psychotic period, exhibited by violent mania, the inclination to attack humans and other animals, confusion, paralysis of throat muscles, and self-biting of the limbs and the hindquarters. The last period, paralysis, involves generalized muscle weakness, difficulty standing, convulsions, tongue prolapse, salivation and finally respiratory paralysis or failure leading to death. Compared with the furious form of rabies, the paralytic form lacks the mad or psychotic phase. Dogs experiencing the paralytic form often live alone, and rapid onset of paralysis and death is common. However, they also exhibit disturbed behavior and will attack and bite other animals or humans. In short, behavioral changes, including an unusually friendly manner, shy or irritated conduct, or increased vocalization, should be noticed in an infected dog. Isolated case reports of rabies survival have been published for cats, dogs, and human beings, but death usually

occurs after a clinical phase of 1-10 days^[17-18]. Dogs often die within two days, while progression in humans is slower.

A definitive rabies diagnosis is typically determined by a post-mortem laboratory test. To confirm rabies in dogs, humans and other animals, the two recommended methods are virus detection and antigen detection. As for both methods, samples should be processed according to international regulations to avoid any contamination. The fluorescent antibody test (FAT) is the primary method recommended by the World Health Organization (WHO) and the World Organizations for Animal Health (OIE) for brain tissue and other specimens. Other suitable methods to detect viral antigen include immunochemical tests, ELISA, and direct blot enzyme immunoassay. Viral growth in cell culture is used to confirm inconclusive results obtained from FAT or negative results when an exposure has been reported. Animal inoculation tests are increasingly being replaced by cell culture, which are as sensitive, less time consuming and more ethically acceptable. Polymerase chain reaction is not presently recommended for routine diagnosis, but may be used for epidemiological investigations or for confirmatory identification in a reference laboratory. Seroneutralization methods such as fluorescent antibody virus neutralization or the rapid fluorescent focus inhibition test are widely used for detecting antibodies against RABV. These methods are based on the neutralization of a given concentration of rabies virus (CVS strain) *in vitro* before inoculating BHK-21 C13 cells, and seroneutralization can be used for post-vaccination control of canine rabies.

Threshold Host Density and Vaccination of Dogs

The rabies virus needs a minimum threshold host density to sustain transmission of the disease in a population^[19]. Once the density of dogs reaches a critical threshold, rabies spreads rapidly, and the spread can be accelerated through animal translocation. A density of 4.5 dogs/km² can lead to endemic rabies in vulnerable populations^[19]. Dogs owned by humans do not have to be registered in China, so the number of dogs must be estimated. Currently the estimate is 80-200 million^[9], which corresponds to an average density of dogs in China of 8-20/km². The density is much higher in rabies-endemic provinces. Reported canine rabies cases are predominantly distributed in the southern provinces of China bordering the Yangtze River.

Relatively few canine rabies cases occur in northern China, largely as a result of the lower human-to-dog ratio in northern China which leads to a lower risk of exposure to rabid dogs.

In the last 60 years, there have been four major epidemics of human rabies in China, each separated by a 10-year interval. The periodic declines of human rabies resulted from culling of dogs rather than mass vaccination, and the periodic epidemics reflect the relationship between the dog population and the incidence of human rabies. The resurgence of human rabies approximately 10 years after the culling of dogs indicates that depopulation of dogs alone cannot prevent and control rabies. Moreover, culling stray dogs is not culturally acceptable in Buddhist regions of the world. Alternatively, the mass vaccination of dogs has been demonstrated as a useful method for preventing human rabies^[20-21]. Thus, a world without rabies does not necessarily mean a world without dogs.

To control and prevent human rabies epidemics, China should focus on the mass vaccination of dogs rather than other rabies approaches such as healthy dog carriers, possible rabies in wildlife, vaccine matching, inferior, or counterfeit vaccines, and seroconversion testing after vaccination. The WHO has determined that vaccination coverage over 70% is needed to control canine rabies^[9]. A relatively adequate dog vaccination program exists in large cities in China, such as Beijing and Shanghai. For example, in 2006, 2007, 2008, and 2009, immunization coverage in Beijing was 55.0%, 53.8%, 67.4%, and 54.4%, respectively. However, in rural areas of China, canine rabies vaccination coverage is <3%^[3,22]. Therefore, current vaccination coverage in dogs in China needs tremendous improvement.

Prevention and Control of Canine Rabies

Past measures, such as dog sterilization and culling, did not prevent the spread of canine rabies. In China, human rabies was effectively under control in the period 1990-1996, largely because of a nationwide rabies vaccination program for dogs that was initiated in 1987^[24]. However, the number of human rabies cases has increased dramatically since 2000, and the recent increase has been high enough to trigger calls for better control and prevention of canine rabies. We recommend a mass dog vaccination campaign for the control of canine rabies, which could substantially decrease the incidence of human rabies cases in China. However, the vaccination of dogs is not enforced in China, and the

relatively expensive rabies vaccine is costly for dog owners. Dogs are bred as a source of extra income throughout China. No laws or regulations currently exist to restrict breeding practices in villages, towns, and small cities. A further complication is that owned dogs are not required to be registered in most rural areas. In addition, dogs are managed by several independent government departments, with registration occurring at local police departments, while animal rabies vaccines are administered by veterinarians. Hence, the lack of good communication or effective strategies for canine rabies in China is not surprising.

PERSPECTIVE

Based on survival conditions and the owner's intentions, dogs can be divided into three groups: pet dogs, guard dogs and stray dogs. The vaccination coverage of pet dogs is likely to be higher than guard dogs and stray dogs. The guard dogs and stray dogs are mostly found in suburban areas and rural areas. Rabies vaccination coverage of dogs in rural areas is low, largely because of poor awareness of rabies and the high cost of vaccination. The estimated immunization coverage of stray dogs is almost zero. The spread of endemic rabies among the huge population of stray and owned dogs is the greatest challenge to the prevention and control of canine rabies in China. Strategies to control and prevent canine rabies should include public education and awareness about rabies, compulsory registration and licensing for all dogs, full pet and guard dog vaccination programs and the elimination of stray dogs or, at least, bringing such dogs under official management. With the above strategies, together with continued support from the Chinese authorities and increased support from international organizations, it is anticipated that China could reach the WHO goal of being free of human rabies by 2020.

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