Title: Pan-lyssaviruses – A Threat

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Abstract

Rabies virus is found worldwide with some exceptions (particularly islands). Some countries have been free of this virus for many years but pan-lyssaviruses or rabies related lyssaviruses can be found even in countries classified as rabies free. These viruses can cause a neurological disease similar to rabies. The global discovery of lyssaviruses is of continued scientific interest and is of importance to both public and animal health. Rabies is majorly circulating within domestic and feral dogs. But, the presence of lyssaviruses in bats is well-established. Although in areas where terrestrial rabies has been eliminated, bat transmitted lyssaviruses remain a constant threat. Infections with these viruses are easily isdiagnosed as rabies. The specific viruses can be identified only with tests based on monoclonal antibodies or by PCR and sequence analyses. This paper reviews what is known of these pan-lyssaviruses, their diversity and threat to life because of emerging behaviour.

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SPECIAL ARTICLE

Pan-lyssaviruses – A Threat...!

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Abstract

Rabies virus is found worldwide with some exceptions (particularly islands). Some countries have been free of this virus for many years but pan-lyssaviruses or rabies related lyssaviruses can be found even in countries classified as rabies free. These viruses can cause a neurological disease similar to rabies. The global discovery of lyssaviruses is of continued scientific interest and is of importance to both public and animal health. Rabies is majorly circulating within domestic and feral dogs. But, the presence of lyssaviruses in bats is well-established. Although in areas where terrestrial rabies has been eliminated, bat transmitted lyssaviruses remain a constant threat. Infections with these viruses are easily misdiagnosed as rabies. The specific viruses can be identified only with tests based on monoclonal antibodies or by PCR and sequence analyses. This paper reviews what is known of these pan-lyssaviruses, their diversity and threat to life because of emerging behaviour.

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Introduction

The global discovery of lyssaviruses is of continued scientific interest and is of importance to both public and animal health. Lyssaviruses are known to cause fatal encephalitis, referred to as rabies. The term rabies has induced terror throughout human history, as the rabies virus (RABV) is the only viral pathogen that is associated with 100% fatality following the onset of the clinical disease.[1] Whilst rabies is predominantly circulating within domestic and feral dog populations globally, the presence of lyssaviruses in bats is well established.[2] Certainly, bat transmitted human RABV is rare, although in areas where terrestrial rabies has been eliminated, bat rabies remains a constant threat, as exemplified by continued human cases of bat rabies across North America.[3]

Wildlife species can also play an important role in the epidemiology of disease, although the paucity of data on wild animal populations, their distribution, and the generally sporadic interactions between different wildlife populations and domesticated carnivore species means that the role of wildlife and the epidemiology of the virus is often unclear. Still, the transmission of the virus between wildlife and domestic terrestrial carnivores is multidirectional, with incursions of domestic dog rabies into fox populations being reported.4The first laboratory confirmation of RABV in a wolf in India was reported from KVAFSU-CVA Rabies Diagnostic Laboratory, WOAH (Formerly OIE) Reference Laboratory for Rabies, Bengaluru.[5] Shimoni bat virus, Aravan virus, Khujand virus, Bokeloh virus and West Caucasian bat virus have been found, to date, only in bats, but might be pathogenic in other species. Additional rabies-related lyssaviruses are likely to exist. Discovery of new lyssa viruses in bats has stimulated research and surveillance efforts to identify additional members of this genus in bat populations. Gannoruwa bat lyssa virus was isolated from the brains of Indian flying foxes in Sri Lanka.6There is also a serological evidence of Lyssavirus infection among bats in Nagaland, India.[7]

Pan-lyssaviruses

Closely related lyssaviruses, which are known as rabies-related lyssaviruses or non-rabies lyssaviruses, can cause a neurological disease identical to rabies. Lagos bat virus, Duvenhage virus, European bat lyssavirus (EBLV) 1, EBLV 2, Australian bat lyssavirus (ABLV), Mokola virus and Irkut virus have caused clinical cases in humans or domesticated animals,

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and Ikoma virus was detected in the brain of an African civet (Civettictiscivetta) with neurological signs. Shimoni bat virus, Aravan virus, Khujand virus, Bokeloh virus and West Caucasian bat virus have been found, to date, only in bats, but might be pathogenic in other species. Additional rabies-related lyssaviruses are likely to exist.

Antigenicity

The genus Lyssavirus within the family Rhabdoviridae, order Mononegavirales constitutes a growing number of viral pathogens that have been characterized and officially classified. Currently, the lyssavirus genus includes 17 recognized and one related, unclassified virus species,[8-9] which based upon genetic, immunologic, and pathologic characteristics of certain members can be assigned to at least three distinct phylogroups.[10-12] Phylogroup 1 includes Rabies lyssavirus, Duvenhage lyssa virus, European bat lyssa viruses, type 1 and 2, Taiwan bat lyssa virus, Bokeloh bat lyssavirus and Australian bat lyssa virus. Also, Aravanlyssa virus, Khujandlyssa virus, Irkut lyssavirus and Gannoruwa bat lyssa virus (GBLV) are members of phylo group 1. Phylo group 2 includes Lagos bat lyssavirus, Mokola lyssavirus and Shimoni bat lyssavirus. West Caucasian bat lyssa virus, Ikoma lyssavirus and Lleida bat lyssavirus are the most divergent viruses in the genus which form independent phylo group 3. In August 2017, a dead Brandt's bat (M. brandtii) was found in Eastern Finland in the village of Kotalahti. The bat tested positive for rabies in the fluorescent antibody test (FAT) and while virus isolation was unsuccessful, RT-PCR and subsequent phylogenetic analysis revealed that the virus differed from other known lyssaviruses and was designated as Kotalahti bat lyssavirus (KBLV).[13] Kotalahti bat lyssavirus (KBLV), a related and unclassified virus species is most closely related to EBLV-2 (78.7% identity), followed by KHUV (79.0%) and BBLV (77.6%), supporting the assignment as phylo group I lyssavirus. Interestingly, all of these lyssaviruses were also isolated from bat species of the genus Myotis, thus supporting that M. brandtii is likely the reservoir host.[14] All lyssaviruses are assumed to be capable of causing rabies, i.e., an infection of the central nervous system that inevitably lead to lethal encephalitis.[15]

Antigenic cross-reactivity correlates with the relatively short genetic distances between lyssa viruses. Antigens of the RNP, which are most abundant in infected cells, cross-react between all members of the genus described to date. This feature facilitates the use of standardised diagnostic reagents for detection of all lyssaviruses (e.g., by direct fluorescent antibody or immunohistochemical assays). In contrast, glycoprotein antigens are relatively conserved within phylo groups (ectodomain conservation >75%) but not between phylo groups (<65%). As a result, commercially available rabies vaccines and anti-rabies immunoglobulins, that mainly induce or provide neutralising antibodies targeting the glycoprotein, protect against phylo group I lyssaviruses but not against other lyssaviruses.

Methods used to determine phylo groups

The classification of lyssaviruses has evolved over time. Initially lyssaviruses were subdivided into serotypes based on their assorted cross-reactivities in classical serologic assays.[16] However, the introduction of monoclonal antibody techniques and later molecular typing provided a much improved level of resolution of this genus. Presently, lyssavirus species can be grouped into phylo groups based on sequence and phylogenetic analysis, each with unique genetic, immunogenic and pathogenic properties.[10] The phylo group II viruses diverge more at the amino acid level on the glycoprotein gene. West Caucasian bat virus may represent a new phylogroup; however, only a single isolation of this virus has been reported, thus precluding official designation.[17]

Species affected

With the possible exception of Mokola virus, rabies related lyssaviruses seem to be maintained in insectivorous bats and fruit bats. They also cause illness in these animals. Mokola virus has been detected in shrews and wild rodents, but not bats, and its reservoir host is still uncertain. The reservoir host for Ikoma virus is also unknown. The susceptibility of other mammalian species to rabies related lyssaviruses is incompletely understood. Like rabies virus, these viruses might be able to infect all mammals. As of 2012, fatal neurological disease has been reported in cats, dogs and a water mongoose (Atilaxpaludinosis) infected with Lagos bat virus; cats and dogs infected with Mokola virus; cats, sheep and a stone marten infected with EBLV 1; and an African civet infected with Ikoma virus.

Zoonotic potential

All rabies variants are thought to be zoonotic. Clinical cases have also been caused by Duvenhage virus, EBLV 1, EBLV 2, Australian bat lyssa virus, Mokola virus and Irkut virus. Humans are likely to be susceptible to other rabies related lyssa viruses.

Geographic distribution

Rabies related lyssaviruses have been found only in the Eastern Hemisphere. There is limited information on the distribution of individual viruses within this area. EBLV 1, EBLV 2 and Bokeloh virus occur in Europe, Irkut virus and West Caucasian bat virus were detected in Russia, and Aravan virus and Khujand virus have been found in Asia. Antibodies to West Caucasian bat

virus were also found in Africa, suggesting that it or a related virus might circulate there. Viruses that have been reported only from Africa include Duvenhage virus, Lagos bat virus, Mokola virus, Shimoni bat virus and Ikoma virus. Australian bat lyssavirus seems to be limited to Australia, but neutralizing antibodies to this or a related virus were found among bats in the Philippines. Rabies-related lyssaviruses have not been detected in the Americas, where the classical rabies virus is common among bats. The presence of a rabies-related lyssavirus does not prevent a nation from being listed as rabies-free.

Transmission

There is little information on the transmission of rabies related lyssaviruses, although it is probably similar to rabies. Infections with these viruses have been reported after bites, scratches or close contact with bats. Bats inoculated with Eurasian bat lyssaviruses shed virus in saliva shortly before clinical signs developed. In one experiment, there was no evidence for transmission to uninoculated bats kept in the same cage.

Diagnostic tests

Infections with rabies-related lyssaviruses are easily misdiagnosed as rabies. The immunofluorescence test used for post-mortem rabies diagnosis can detect these viruses, but does not recognize them as different from rabies virus. The specific virus can, however, be identified with tests based on monoclonal antibodies, or by PCR.

yssa viruses show broad antigenic cross-reactivity at the nucleocapsid level, mainly because of sequence conservation of the N protein. The standard diagnostic test consists of direct fluorescent antibody (DFA) testing of impressions made from fresh brain tissue (i.e., cerebellum, hippocampus and brain stem). When performed properly, no other laboratory test for the diagnosis of rabies is as simple, sensitive, specific, inexpensive and rapid as the DFA test performed on fresh brain tissue.18 This allows the use of similar reagents for diagnosis by immunofluorescence and is the method of choice used by U.S. public health laboratories for routine diagnosis of rabies virus infection.19

Monoclonal antibodies for characterization of rabies viruses are useful in distinguishing rabies virus and its close relatives. Once a monoclonal antibody is raised against a particular virus, it can be used to probe related viruses to determine how specifically it binds. An antigenicity profile can be generated using a panel of monoclonal antibodies raised against different isolates. These studies have demonstrated that rabies virus is distinguishable from related lyssavirus genotypes and that rabies virus isolates from a given geographic area or those belonging to different species have unique reactivity patterns, both due to common epitopes within the viral ribonucleoprotein core and to the glycoprotein components of the virion.

Treatment and control

All currently licensed vaccines are based on rabies virus, and do not contain antigens from other lyssaviruses. Nevertheless, limited, preliminary studies in animals suggest that these vaccines may provide some protection against other phylo group I viruses. In Europe, vaccination is recommended for people who regularly handle bats and may be exposed to lyssaviruses. Precautions should also be taken to avoid bites and scratches. If an injury occurs, the wound should be cleansed and brought to the attention of a physician. Some sources recommend rabies booster vaccination/ post-exposure prophylaxis if the bat is not available for testing.

Conclusion

A staggering 99% of human cases are acquired via the bite of an infected dog, rather than through exposures to the many and varied wild animals including bats that act as viral reservoirs on different continents. But closely related lyssaviruses circulate among bats in the Eastern Hemisphere, and can cause an illness identical to rabies in people and domestic animals. Rabies vaccines and post-exposure prophylaxis are thought to provide some protection against some of these viruses, but not others. Additional rabies-related lyssaviruses are likely to exist.

Infections with pan-lyssaviruses seem to be rare, but might be under diagnosed, as the symptoms are similar to rabies and many of the commonly used tests do not distinguish these viruses. Monoclonal antibodies and sequence analyses are the choice for the diagnosis of these pan-lyssaviruses. Almost all reported cases have been fatal. Although some rabies-related lyssaviruses seem to be relatively common in bats, only a few clinical cases have been reported in domestic animals.

In India, there are scanty reports on pan-lyssaviruses. But, the serological evidence of Lyssavirus infection among bats in Nagaland and the isolation of Gannoruwa bat lyssa virus from the brains of Indian flying foxes in Sri Lanka, fuelling researchers to give more emphasize on the study of epidemiology and disease dynamics of rabies-related lyssaviruses in wild animals prioritizing bats.

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