GUIDELINE for Feline rabies

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Introduction

Rabies is one of the oldest and most feared diseases of humans and animals – it was recognized in Egypt before 2300 BC and in ancient Greece, where it was well described by Aristotle. Perhaps the most lethal of all infectious diseases, rabies also has the distinction of having stimulated one of the great early discoveries in biomedical science. In 1885, before the nature of viruses was comprehended, Louis Pasteur developed, tested, and applied a rabies vaccine, thereby opening the modern era of infectious disease prevention by vaccination.

Agent properties

Rabies virus (RABV) is a member of the Rhabdoviridae family. The genus Lyssavirus contains 16 species (Amarasinghe et al., 2018). According to antigenic properties and phylogenetic relationships, viruses in the genus have been divided into two phylogroups. Phylogroup I includes RABV, Australian bat lyssavirus (ABLV), Duvenhage virus (DUVV), European bat lyssavirus 1 (EBLV-1), European bat lyssavirus 2 (EBLV-2), Aravan virus (ARAV), Khujand virus (KHUV), Bokeloh bat lyssavirus (BBLV) and Irkut virus (IRKV); phylogroup II includes Lagos bat virus (LBV), Mokola virus (MOKV) and Shimoni bat virus (SHIBV) (Badrane et al., 2001, Fooks et al., 2004). The most divergent viruses in the genus, West Caucasian bat lyssavirus (WCBV) and Ikoma virus (IKOV), are not members of either of these phylogroups. Each of these viruses is considered capable of causing rabies-like disease in animals and humans.

Antigenic cross-reactivity between lyssaviruses correlates with the genetic distances between them. Nucleoprotein antigens, which are most abundant in infected cells, cross-react between all members of the genus described to date. This facilitates the use of the same reagents for immunological detection of all lyssaviruses. In contrast, glycoprotein antigens are relatively conserved within phylogroups (ectodomain conservation >75%) but not between phylogroups (ectodomain conservation <65%). Therefore, commercially available rabies vaccines, inducing neutralizing antibodies against the RABV glycoprotein, partially protect against other phylogroup I lyssaviruses but not against other lyssaviruses (Lefkowitz et al., 2017; Nokireki et al., 2017; Echevarría et al., 2019; Servat et al., 2019).

Rhabdoviruses can be stable in the environment especially at alkaline pH but are thermolabile and sensitive to the UV irradiation of sunlight. In clinical practice, rabies virus is easily inactivated by detergent-based disinfectants. Virions are formed almost exclusively in salivary gland epithelial cells. The replication of rabies viruses is slow and usually non-cytopathic. Rabies virus produces prominent cytoplasmic inclusion bodies (Negri bodies) in infected cells.

Laboratory-adapted (“fixed”) rabies virus replicates well in Vero (African green monkey kidney) cells and BHK-21 (baby hamster kidney) cells, which are the most common substrates for growing animal rabies viruses for vaccine production. Rabies virus also replicates to high titer in suckling mouse and suckling hamster brain.

Epidemiology

The disease occurs worldwide, with certain exceptions. The rabies situation and the regulations are continuously updated on the web sites of the OIE and WHO. The number of annual human deaths is estimated at approximately 40,000 to 100,000 worldwide, and more than 15 million people receive post-exposure treatments after being exposed to suspected rabid animals.

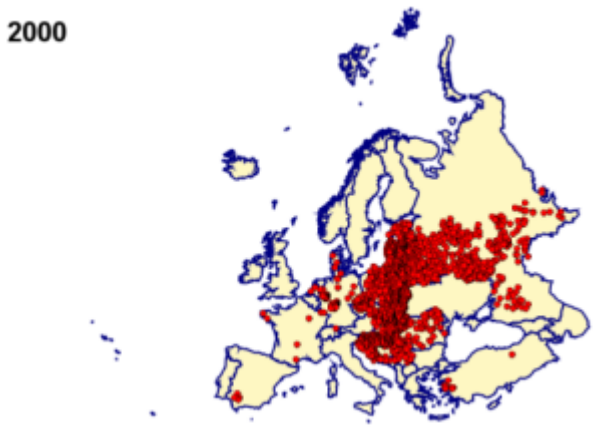
In many countries of Asia, Latin America and Africa, endemic dog rabies is a serious problem, causing significant domestic animal and human mortality. In these countries, human vaccines are used in large numbers of doses, and there is a continuing need for comprehensive, professionally organized and publicly supported rabies control agencies. That such agencies are not in place in many

developing countries is a reflection of their high cost; nevertheless, progress is being made. For example, a substantial decrease in rabies incidence has been reported in China, Thailand and Sri Lanka, following implementation of dog vaccination programs and improved post-exposure prophylaxis of humans. Similarly, the number of rabies cases in Latin America is declining significantly. Strictly enforced quarantine of dogs and cats for various periods before entry has been used to effectively eliminate terrestrial (i.e. not bat-transmitted) rabies from Japan, the United Kingdom (UK), New Zealand and several other islands. In contrast, rabies was not recognized in Australia until recently, when the Australian bat lyssavirus was discovered, and subsequently found to be endemic in south-east Australia.

In most industrialized countries, even those with a modest disease burden, publicly supported rabies control agencies operate in the following areas: (1) programs of oral vaccination of wildlife, in Europe of the red fox; (2) stray dog and cat removal and control of the movement of pets (quarantine is used in epidemic circumstances, but rarely); (3) immunization of dogs and cats, so as to break the chain of virus transmission; (4) laboratory diagnosis, to confirm clinical observations and obtain accurate incidence data; (5) surveillance, to measure the effectiveness of all control measures; and (6) public education programs to assure cooperation.

In Europe, the red fox is the main reservoir species of rabies. As a result of wildlife vaccination programs large regions in Europe became free of terrestrial rabies (Fig. 1). The incidence of animal rabies in Europe 2019 is presented in table 1.

Distribution map for animal terrestrial rabies in Europe, 1990



Distribution map for animal terrestrial rabies in Europe, 2000

Distribution map for animal terrestrial rabies in Europe, 2010

2019

Distribution map for animal terrestrial rabies in Europe, 2019

Fig. 1. The success of rabies control in Europe. Source: World Health Organization (www.who-rabies-bulletin.org)

Tab. 1 Animal rabies cases in Europe 2019. Source: World Health Organization (www.who-rabies-bulletin.org)

COUNTRY	NUMBER OF RABIES CASES	
	in animals other than bats	in bats
France	0	9
Georgia	50	0
Germany	0	9
Italy	1	0
Latvia	1	0
Moldova	81	0
Norway	1	0

COUNTRY	NUMBER OF RABIES CASES	
Poland	1	10
Romania	4	0
Russian Federation	547	0
Spain	2	1
The Netherlands	0	5
Turkey	513	0
Ukraine	1426	1
United Kingdom	0	4
Total	2627	39

As a result of the mass vaccination of dogs, cats have become the companion animal species most commonly reported as rabid in many areas affected by wildlife rabies, as is the case in many states of the USA (Gerhold and Jessup, 2013). In a report from Pennsylvania, among 2755 rabid animals with reported human exposure, as many as 799 (29.0 %) were free-ranging cats, whereas only 57 (2.1 %) were dogs (Campagnolo et al., 2014). Also in Europe the cat has been considered in endemic areas to be a high-risk species for transmission of rabies from wildlife to human beings. For example, in the past of more than 20,000 inhabitants in Switzerland that had to be vaccinated after exposure to rabies, around 70% had been either bitten or in close contact with cats (Hohl et al., 1978). Even if feline rabies is considered to be a by-product of canine or wild rabies (Blancou and Pastoret, 1990), behavioural characteristics of cats and clinical aspects of the disease in this species render it important for public health reasons. In fact, despite a lower number of post-exposure prophylaxis treatment for people following cat bites compared to dog bites, treatment was justified more often (Blancou and Pastoret, 1990).

There is increasing evidence that lyssaviruses are able to circulate within bat populations in the absence of disease (Banyard et al., 2011). Figure 2 shows a map of bat rabies cases in Europe 2010-2019. EBLV-1 is associated with more than 95% of the infected bats diagnosed in Europe (Echevarría et al., 2019). Four other lyssaviruses have been found in European bats: EBL-2, BBLV (Eggerbauer et al., 2017), Lleida bat lyssavirus (LLEBV) (Picard-Meyer et al., 2019) and Kotalahti bat lyssavirus (Nokireki et al., 2018). In November 2007, a cat in France died of rabies as a result of infection with bat lyssavirus. In 2020, a cat after a suspected exposure to bats tested positive for the WCBV in Italy (https://www.izsvenezie.it/caso-lyssavirus-gatto-comune-arezzo/). However, although rabid bats have been reported in the UK (Johnson et al., 2003; Fooks et al., 2004) and the Mammal Society estimates that British cats could be killing 230,000 bats a year (Woods et al., 2003), no cases of cat rabies have been documented in the UK. These findings indicate that the risk of cats becoming infected with rabies from bats might be very low.

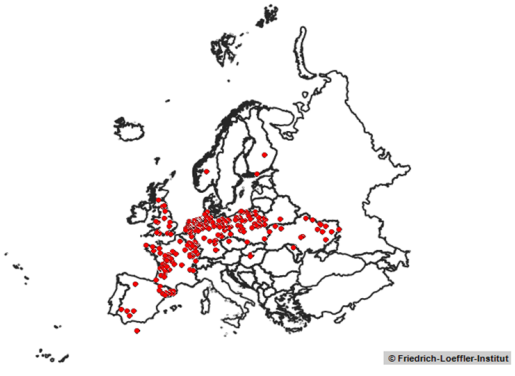


Fig. 2. Distribution map for bat rabies cases in Europe 2010-2019 (www.who-rabies-bulletin.org)

Another risk for European regions free of terrestrial rabies is cross-border reinfection by foxes from endemic European countries, as happened in Italy 2008, in the Republic of Macedonia 2010, in Greece 2012 and in Slovakia 2013 (Ribadeau-Dumas et al., 2016). Finally, illegal importation of pets from regions where the disease is endemic poses an increasing risk (BBC, 2014). During 2001–2013, a total of 21 animal rabies cases attributed to pets from rabies-enzootic countries were reported in western Europe, introduced mostly from Morocco (Ribadeau-Dumas et al., 2016). Another concern is that inappropriate rabies vaccination in some exporting countries could make rabies a risk connected even with legal importation of pets. Several studies found an extraordinary high proportion of vaccination failures among dogs imported from Eastern Europe (Klevar et al., 2015; Rota Nodari et al., 2017). Recently, among 36 dogs imported into Finland with documents confirming rabies vaccination in the Russian Federation or Romania, 19 had an antibody level < 0.5 IU/mL, whereas in the control group of 36 dogs born, raised and vaccinated in Finland only two had such a level (Kaila et al., 2019). The finding in this study that 39% of the imported dogs had antibody levels < 0.1 IU/mL suggested that at least some of them might not have been vaccinated at all.

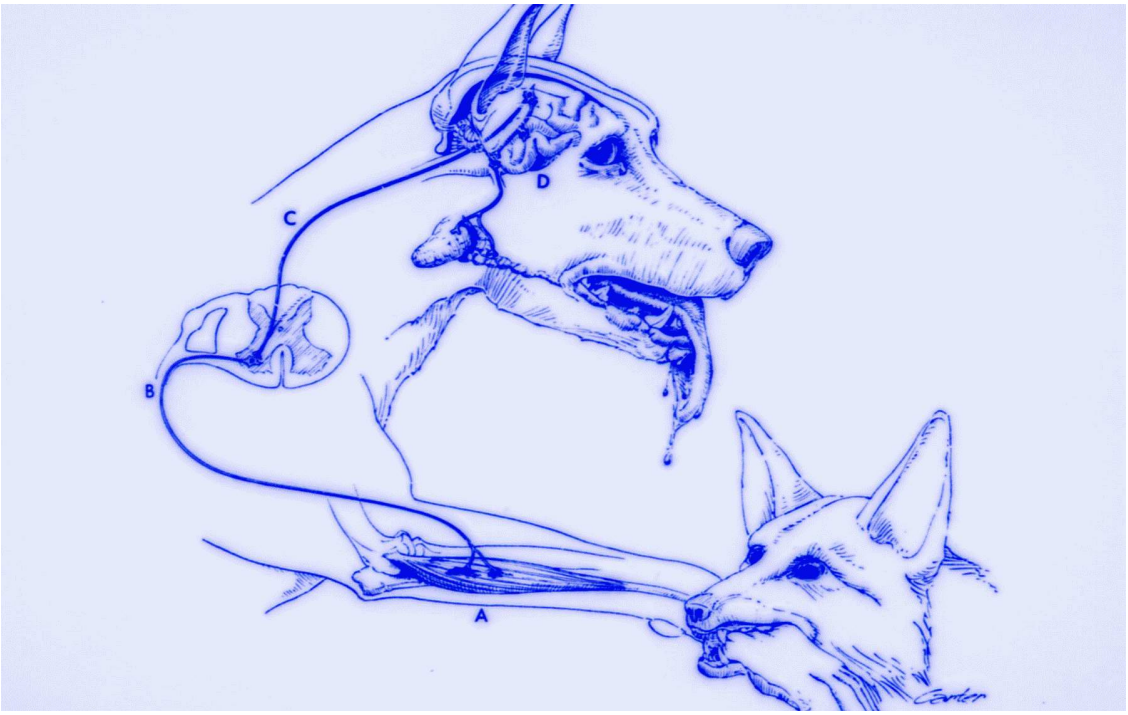


Fig. 3. Rabies transmission from fox and pathogenesis of the infection in the dog – didactic poster

Pathogenesis

Rabid animals are the only source of virus. It is shed in the saliva some days before the onset of clinical signs, and the agent is transmitted through a bite (Fig. 7) or a scratch of the skin or mucous membranes (eyes, nose, mouth). The blood of rabid animals is not infectious.

The average incubation period in cats is two months, but can range from two weeks to several months or even years, depending on the dose of virus transmitted and the severity and site of the wound (Charlton et al., 1997; Jackson, 2002). The incubation period is variable because the virus moves along peripheral nerves with the normal axoplasmic flow from the inoculation site to the central nervous system (CNS): hence the greater the distance from the CNS, the longer the incubation period; and the greater the density of innervation of the inoculated tissue, the shorter this duration (Greene and Rupprecht, 2006).

Very long incubation periods have been described in some experimental cases (Murphy et al., 1980), which must be taken into account when evaluating wound history, especially in free-roaming cats exhibiting sudden behavioural change and/or signs of motor neuron dysfunction that can initiate the clinical phase. The virus replicates in striated muscle and connective tissue at the site of inoculation

and then enters the peripheral nerves through the neuromuscular junction (Murphy et al., 1973). Alternatively, it can infect peripheral nerves directly, spreading to the CNS via the axonal route.

The virus then travels to the salivary glands by the retrograde axonal route. At this time, the animal becomes infectious, i.e., about 3 days before the first clinical signs appear. By that time, the virus is widely disseminated throughout the organs. In most cases, death occurs within 5 days so that a cat or a dog will be shedding the virus in saliva for about 8 days in total.

Most clinical signs are related to the virus-induced central and peripheral nervous system dysfunction rather than neuronal death, and abnormalities in neurotransmission have been described (Jackson, 2002).

Immunity

Passive immunity

Kittens from vaccinated queens obtain maternally derived antibodies (MDA) via the colostrum. The MDA titer in kittens depends on both the antibody level of the queen and the amount of colostrum ingested during the first day of life. In most kittens, MDA will not persist for longer than 12 weeks. MDA have been demonstrated even in the sera of fox cubs whelped by orally immunized vixens (Vos et al., 2003). Passive immunity can neutralize vaccine virus, thereby inhibiting immunoglobulin production and interfering with immunization during the first weeks of life. Therefore, it is generally recommended to perform the primary vaccination in kittens over 12 weeks of age.

Active immunity

Rabies virus antigens are highly immunogenic and capable of eliciting the full spectrum of protective immune responses. The virus is not cytopathogenic, cells are not destroyed during its replication or maturation, and low levels of antigen are presented to the immune system. Neither humoral nor cell-mediated specific responses can be detected during the early stages of movement of virus from the site of the bite to the CNS (Green, 1997). Hence, infection of naive animals with rabies virus most often results in disease and death. Such sequel can be averted by prompt immunization following exposure, demonstrating that the development of anti-rabies viral immunity prior to extensive infection of neurons is protective.

It is well documented that neutralizing antibodies are crucial in this immunity. Rabies is an example of a “Th-2 healing disease”, where activation of B lymphocytes with the help of CD4 T cells is important for protection. When activated, primarily by the viral nucleoprotein, CD4 T cells produce cytokines (IL-4) that stimulate B cells to produce antibodies. In contrast, rabies-specific CD8 T cells cause neuronal damage when a Th-1 response (IFN-γ and TNF-α) predominates (Lafon, 2002; Hooper, 2005). However, vaccinated animals without detectable virus neutralizing antibodies have survived rabies challenge, indicating that other mechanisms could also protect against this disease (Aubert, 1992; Hooper et al., 1998).

After intramuscular infection, the virus replicates locally for several weeks in the myocytes or nervous tissue. In vaccinated cats with adequate serum antibody titers, the virus is often neutralized during this early incubation period. In contrast, unvaccinated cats exposed to rabies virus can produce an antiviral immune response, usually late in the clinical course, that fails to prevent disease (Johnson et al., 2006). However, protection against the early stages of infection is provided by innate immunity, in which interferon seems to play a critical role. High levels of interferon are detectable in sera of mice inoculated with rabies virus by peripheral or intracerebral routes (Marcovistz et al., 1984, 1994; Johnson et al., 2006).

It is not clear how effective these mechanisms are in naturally exposed naive cats. It is believed that factors determining morbidity include the amount and strain of the virus, the age and immunocompetence of the cat, and the site of the bite; in unvaccinated cats the risk of developing rabies is higher (and the incubation period shorter) in a young animal that has been bitten severely in the head, with a high saliva deposit in the wound, as compared to an adult cat bitten in a limb, especially after extensive bleeding (Pastoret et al., 2004).

If clinical signs are evident, recovery from rabies is exceedingly rare. There have been very few reports of cats, dogs and humans that have recovered following confirmed clinical rabies (Bernard, 1985; Fekadu, 1991; Netravathi et al., 2015). Furthermore, antibodies to lyssaviruses have been detected occasionally in domestic or wild cats with no history of vaccination, suggesting a non-fatal disease or subclinical infection (Tjørnehøj et al., 2004; Deem et al., 2004; Gold et al., 2020). Although rabies is prevalent among lions’ prey and food competitor species, there have only been a few reported deaths in lions (Swanepoel et al., 1993). Lions might be less susceptible to the disease and acquire protective antibodies from natural infection (Lutz, 2011; http://www.research-projects.uzh.ch/p14931.htm; Berentsen et al., 2013). Also in spotted hyenas (Crocuta crocuta) an antibody prevalence of 37 % was shown, perhaps resulting from the transmission of small infectious doses, e.g. due to the hyenas’ particular behaviour of licking anothers’ muzzles as a greeting behavior (East et al., 2001).

Clinical signs

Aggressive behaviour towards humans is unusual in healthy cats, so any unjustified aggression in cats must be considered highly suspicious. Rabies should be suspected not only when there has been a recent history of a bite by or exposure to a rabid animal but also where an unvaccinated cat might have been in contact with potentially infected wildlife, such as bats.

Fig. 4. Rabid cat, furious syndrome. Courtesy of Andy Sparkes and AFFSA/ERZ (inset)

Two disease forms can be identified in cats: the furious and the dumb form. The furious form (Fig. 4) has three clinical phases (prodromal, furious or psychotic and paralytic) but they are not always distinct. The dumb form (Fig. 5) has two phases: prodromal and paralytic. During the very short prodromal phases (12-48 hours) of both forms, a wide range of quite non-specific clinical signs (fever, anorexia, vomiting, diarrhea) can occur, sometimes accompanied by neurological signs. Behavioural changes can be noticed first, such as an unusually friendly or otherwise shy or irritated behaviour and increased vocalization. Altered behaviour depends on forebrain involvement and can be associated with other neurological signs reflecting the infection site.

Fig. 5. Rabid cats. Courtesy of Artur Borkowski, AFFSA/ERZ, and Merial S.A.S.

If the bite occurs in the face, clinical signs reflect cranial nerve and forebrain involvement: the former can produce depressed or absent

reflexes (palpebral, corneal, pupillary etc.), strabismus, dropped jaw, inability to move whiskers forward, dysphagia, laryngeal paralysis, voice change, tongue paralysis. Forebrain involvement is responsible for seizures, muscular twitching or tremors, aimless pacing, exaggerated emotional responses (irritability, rage, fearfulness, photophobia, attacking inanimate objects etc). The tendency to bite can be the consequence of the loss of inhibitory control by cortical neurons over the subcortical bite reflex; dogs and cats then turn and snap at anything that touches them around the mouth (O'Brien and Axlund, 2005), without warning or showing any emotion. Pruritus at the bite site can be observed.

If the infecting bite was on the limbs, neurological signs start from the spinal cord and an ascending lower motor neuron (LMN) paralysis occurs before the brain signs. The inflammation rapidly spreads throughout the CNS producing severe ataxia, disorientation, paralysis, seizures, status epilepticus, eventually followed by coma and death from respiratory arrest. The furious phase is more consistently developed in cats showing behaviour abnormalities (Fogelman et al., 1993). The paralytic phase (incoordination, paraparesis, generalized paralysis, coma and death) usually begins five days after the first clinical signs and death usually occurs after a clinical course of 1-10 days. Cats often die in 3-4 days (Rupprecht and Childs, 1996), whereas dogs mostly succumb within two days (Tepsumethanon et al., 2004).

Atypical forms of chronic rabies in cats have been described after experimental infection (Murphy et al., 1980).

The serious public health risk (particularly for veterinarians) requires a careful differential diagnosis. Any CNS disease characterized by sudden onset and rapidly evolving clinical signs must include rabies for free roaming, unvaccinated cats living in endemic areas or traveling there. The clinical examination must make safety the highest priority, because manipulation and restraint of the patient could provoke biting – at a time when the salivary glands are already infected and rabies virus is shed. Rabies should be included in the differential diagnosis in live cats in endemic areas with suspected encephalitis, based on anamnestic history and observation when the animal is still in the carrier, to reduce the risk of exposure for the veterinary team (see the flow chart below; Fig. 6).

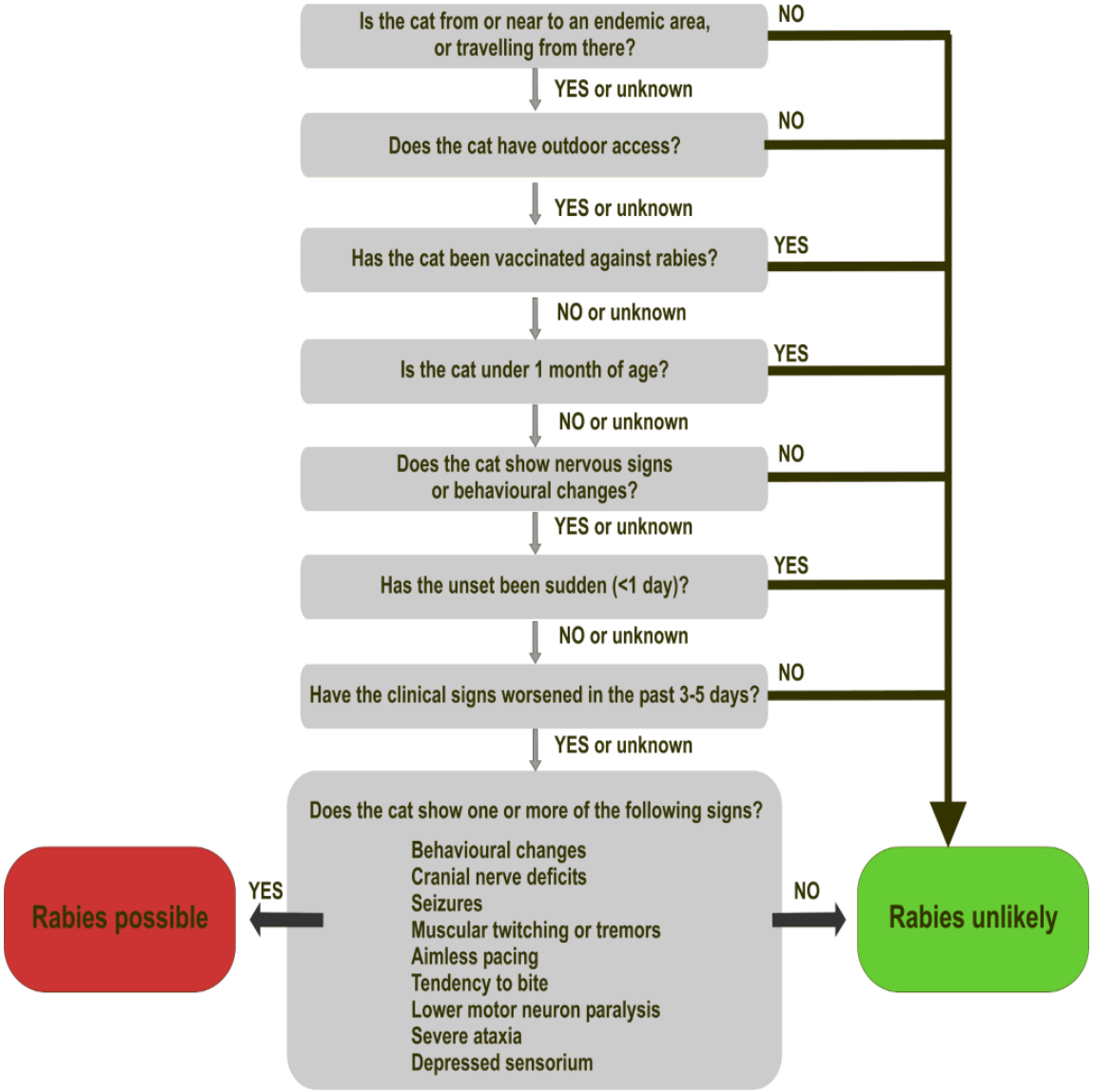


Fig. 6. Assessing the likelihood of rabies, adapted from Tepsumethanon et al., 2003

1. Dramatic behavioural changes, staggering, stumbling
2. Aggressiveness, unprovoked biting

1. Furious form seen in 90 % of rabid cats
2. Deterioration in nutritional status (anorexia)
3. Ruffled and dirty coat (the cat does not clean itself)
4. Mucous membranes, tongue, nose and footpads are reddish pink (high fever)
5. Chin and front legs are wet from salivation
6. Permanent movement and restlessness
7. Imbalanced gait, paresis of the hind legs
8. Pupil dilatation unresponsive to light
9. Abnormal water uptake (water runs from the mouth)
Courtesy Dr Veera Tepsumethanon

Diagnosis

Because a clinical diagnosis of rabies is unreliable, a definitive diagnosis must be obtained by post-mortem laboratory examination.

Antibody tests are used only for surveys and post-vaccinal control in order to test immunity level in vaccinated animals, especially in the context of international movements.

OIE recommendations

Recommendations from experts of the OIE First International Conference “Rabies in Europe” (Kiev, Ukraine, 15-18 June 2005) are:

i) Routine laboratory diagnosis should be undertaken using only the techniques specified by the OIE (Terrestrial Manual – OIE 2019, https://www.oie.int/standard-setting/terrestrial-manual/access-online/) and the WHO (Laboratory Techniques in Rabies)

ii) The Fluorescent antibody test (FAT) is the primary method recommended

iii) The confirmation test should use rabbit tissue culture inoculation test (RTCIT). The mouse inoculation test can be used only if rabbit tissue culture is not available

iv) PCR is presently not recommended for routine diagnosis but could be useful for epidemiological studies or for confirmatory diagnosis only in reference laboratories.

Reference laboratories: The list of reference experts and laboratories can be found on the OIE web site (http://www.oie.int/en/our-scientific-expertise/reference-laboratories/list-of-laboratories/).

Detection of the infectious agent

Direct detection

Only direct detection methods are recommended to confirm rabies in human beings and animals.

Samples (animal heads, brain tissues or other organs) should be sent according to the national and international shipping regulations and care should be taken in order to avoid potential human contamination. Because rabies virus is rapidly inactivated, the specimen should be shipped (preferably) refrigerated or at room temperature in 50 % glycerin in phosphate buffered saline solution.

Brain tissue (especially thalamus, pons and medulla) is the preferred sample for postmortem diagnosis but other organs such as salivary glands can also be used.

The FAT is the method recommended by WHO and OIE for fresh or glycerol samples (Bourhy et al., 1989; Birgham and van der Merwe, 2002), but is less sensitive in formalin-fixed tissues. It provides a reliable diagnosis in 95 to 99 % of cases for all lyssaviruses in fresh samples. It can also be used for rabies detection in cell cultures and in brain tissue of mice that have been inoculated for diagnosis.

Other methods available include immunochemical tests (e.g. avidin-biotin peroxydase system, ELISA, direct blot enzyme immunoassay). The rapid rabies enzyme immunodiagnosis (RREID) is an alternative to FAT but detects only the rabies virus, but not other lyssaviruses. Correlation between FAT and RREID is between 96 and 99% (Barrat, 1993).

These tests are used to confirm inconclusive results with FAT in organs or when FAT is negative if human exposure has been reported.

Intracerebral inoculation of mice is performed in newborn or 3 to 4 week-old mice. FAT is used to detect virus 5 to 11 days post-inoculation. Ideally, these inoculation tests should be replaced by cell culture tests, which are as sensitive, less time-consuming and more ethical. Neuroblastoma cell lines could be used and presence of the rabies virus is revealed by FAT, with results being available within 2 to 4 days.

Since histology and immunohistochemistry to detect Negri bodies are less sensitive than FAT, especially in autolysed tissues, these methods are not recommended for routine diagnosis.

Reference laboratories can identify rabies virus, especially variants, using monoclonal antibodies, nucleic acid probes or PCR and sequencing. These techniques can distinguish vaccine and field strains and may identify the geographic origin of the isolate.

Indirect detection (Antibody Tests)

Seroneutralisation tests in cell cultures, such as fluorescent antibody virus neutralisation (FAVN) or rapid fluorescent focus inhibition test (RFFIT) are widely used to confirm immunity induced by vaccination. The principle of FAVN is neutralisation in vitro of a rabies CVS strain before inoculating BHK-21 C13 cells. The titer is expressed in international units (IU/ml) and is the reciprocal value of the dilution at which 100% of the virus is neutralised in 50 % of the wells. RFFIT and FAVN give equivalent results. A value of 0.5 IU/ml of serum antibodies is the internationally accepted threshold titer.

ELISA is used for testing vaccinated animals (Servat et al., 2007). Commercial kits are available for the detection of antibodies in sera from vaccinated cats and dogs. Commercial ELISA tests can be conducted without culturing of live virus, and results can be obtained within 4 hours. Sensitivity and specificity of the ELISA still need to be confirmed before it can be accepted as an official method (Servat et al., 2006). For further details, refer to Barrat et al. (2006) and the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (OIE, 2019).

Rabies control in cats

Treatment (post-exposure vaccination)

The allowance to perform post-exposure vaccination of healthy cats depends on the national regulations. In case of clinical suspicion, the animal should be safely confined, and competent authorities should be notified. No supportive or specific treatment has proved to be effective in rabid cats, so treatment is not recommended (Greene and Rupprecht, 2006), and highly contraindicated due to public health risk. Detailed recommendations for animal rabies prevention and control in the USA have been published a few years ago (Brown et al., 2016).

Prophylaxis (preventive vaccination)

Because of the public health risk associated with susceptible domestic cats becoming infected following exposure to rabid animals, all cats with outdoor access in endemic areas (e.g. Ukraine, Russia, Turkey) should be vaccinated. The vaccine should be administered in accordance with local or state regulations and considering the epidemiological situation. In countries where rabies is absent, vaccination is indicated when the cat moves or travels abroad (see “Rabies vaccination and cat movement within the EU”) or to an area where rabies is endemic.

In the past, when modified-live vaccines were used, vaccine-induced rabies cases were sporadically observed also in cats (Whetstone et al., 1984). Neurological signs occurred several weeks after vaccination and were characterized mostly by progressive upper motor neuron limb paralysis and cranial nerve deficits. Now rabies in cats is usually controlled by traditional inactivated vaccines (OIE, 2019) and several products are available commercially. They are very efficient and generally considered to be safe, even in neonatal kittens. Though differences in the efficacy between some commercial rabies vaccines used in Europe have been demonstrated (Minke et al., 2009; Zanoni et al., 2010; Berndtsson et al., 2011), following a single vaccination these products have been shown to induce in most animals a titer above 0.5 IU/ml what is an internationally accepted threshold antibody level (Fu, 1997; Perez and Paolazzi, 1997; Minke et al., 2009; Van de Zande et al., 2009; Berndtsson et al., 2011). Cats and dogs with such a titer, regardless of the period of time elapsed since vaccination, have a very high probability of survival after a rabies infection (Cliquet, 2006).

Cats respond better to rabies vaccination than dogs and only 2.6% of cats develop titers below 0.5 IU/ml after the first vaccination (Cliquet, 2006). As tested 6 to 12 months post vaccination this proportion was about 8 % (Zanoni et al., 2010). After the first vaccination many cats develop titers even above 5 IU/ml (Cliquet, 2006). In cats and dogs, the peak of rabies neutralizing antibodies is generally reached between 4 to 8 weeks after the first immunization (Cliquet, 2006; Minke et al., 2009).

A very small proportion of cats identified with rabies have had at least one rabies vaccination during their lifetime (Greene and Rupprecht, 2006). Since the new EU regulations in pet movement were put in place in 1993, no single case of rabies in a vaccinated cat has been documented (Cliquet, 2006).

Nevertheless, the titer decreases with time. In an epidemiological study among thousands of dogs tested 120 to 360 days post vaccination the proportion of animals with a titer below 0.5 IU/ml was 12.6 %, or 3.1 %, depending on the vaccine brand used (Berndtsson et al., 2011). There is increasing evidence that the persistence of antibodies after the first rabies vaccination might be much shorter than generally believed, especially in dogs. It has been demonstrated that antibody titers fall below 0.5 IU/ml in almost 21 % of dogs within 4-6 months after a single vaccination (Van de Zande et al., 2009), and in many puppies it happens as early as after 56 or even 28 days (Minke et al., 2009). In another study the proportion of dogs with titers below 0.5 IU/ml reached 6 months after the first vaccination 30 % and then stabilized at above 30 % during the next 6 months (Zanoni et al., 2010). However, even if the titer is below 0.5, it does not mean that the animal is unprotected.

Thus, a regimen for rabies vaccination consisting of double primary vaccination with a short interval of 7 – 10 days and a one-year booster has been postulated (Zanoni et al., 2010). This procedure reduced the proportion of cats developing a titer below 0.5 IU/ml to almost nil as tested within 6 months, and in dogs this proportion was also significantly lower than in animals with single primary vaccination (Zanoni et al., 2010).

All cat and dog sera with a titer above 5 IU/ml neutralise EBL-1 and EBL-2 regardless of vaccine virus strain and among sera with a titer between 0.5 and 5 IU/ml 87 % neutralise EBL-1 and 53 % EBL-2 (Fooks, personal communication). However, against some novel lyssaviruses isolated from bats in Eurasia the protection might be reduced or negligible depending on the genetic distance between the new isolate and the rabies virus (Hanlon et al., 2005; Lefkowitz et al., 2017).

Inactivated vaccines can carry a risk due to the remote possibility of incomplete inactivation of the virus and the inadvertent spread of residual pathogenic particles of rabies virus (Schneider, 1995). Furthermore, inactivated rabies vaccines containing adjuvants can be associated with the development of injection site sarcomas in cats (Dubielzig et al., 1993). Such problems led to continued efforts to develop safer rabies vaccines. New vaccines include recombinant subunit proteins (Wunner et al., 1983), recombinant viral vectors

(Paoletti, 1996; Xiang et al., 1996) and DNA-based vaccines (Osorio et al., 1999; Cupillard et al., 2005).

Recombinant live vector vaccines have some advantages over traditional products: they are innocuous, they induce suitable humoral immune responses and they do not require rabies virus to be handled (Paoletti, 1996). They also induce less inflammation at the site of injection (Day et al., 2007). A non-adjuvanted recombinant canarypox rabies vaccine for cats has been approved for use in the European Union in 2011.

Primary vaccination course

In contrast to all other inactivated vaccines, a single rabies vaccination induces in most cats a long lasting immunity due to the immunogenic properties of the vaccinal antigen. Kittens should be vaccinated not earlier than at 12 to 16 weeks of age to avoid interference from maternal antibodies, with revaccination one year later (depending on data sheet recommendations for each brand of vaccine). With this schedule, a single vaccination is sufficient in most cats. However, national or regional legislation regarding vaccination type and interval should be adhered too.

Booster vaccinations

Although some commercial vaccines provide protection against virulent rabies challenge for 3 years or longer (Lakshmanan et al., 2006), national or local legislation sometimes require annual boosters.

Vaccination of immunocompromised cats

See ABCD Guideline “Vaccination of immunocompromised cats”.

Disease control in specific situations

Shelters

In endemic areas, stray cats should be always considered at exposure risk and handling or nursing of rescued animals should be considered dangerous even if they are asymptomatic.

Breeding catteries

Risk of exposure is generally almost nil in breeding catteries because many pedigree cats are kept strictly indoors, but their vaccination is under local or state regulation.

Rabies vaccination and cat movement within the EU

The Directive 998/2003 of the European Community established rules for non-commercial (less than 6 animals) movement of pets between EU countries (dogs, cats and ferrets). According to these rules all such animals should be identified by tattoo and/or microchip and vaccinated against rabies, and a 21-day waiting period in case of primary vaccination is required (the vaccination day is not included in this period). Depending on the vaccine used the veterinarian confirms in the passport how long the vaccination will be valid. Any booster within this time will immediately prolong the validation. However, if the booster is performed after the validation date of the last rabies vaccination, a 21-day waiting period before traveling will be required again. In addition, the above regulation provides that some countries maintain their national provisions for a transitional period. In this case, before entry of the country an individual serological test for rabies neutralizing antibodies is required demonstrating that the titer is at least 0.5 U/ml.

As the national requirements are changing, the actual legislation must be checked and followed in case of international pet movement.

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