FECAVA SYMPOSIUM*

CLINICAL ASPECTS OF RABIES: WHAT WILL WE SEE IN OUR CLINICS AND HOW SHOULD WE PROTECT OURSELVES?

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SUMMARY

Rabies is one of the most important zoonotic diseases in the world. The disease affects domestic and wild animals, and is spread to people through close contact with infectious material, usually saliva, via bites or scratches.

AETIOLOGY AND EPIDEMIOLOGY

Rabies has been recognized for centuries. Louis Pasteur identified a virus as the cause of the disease in 1880s. Rabies is present on all continents with the exception of Antarctica. In Europe, foxes are the main reservoir while in North America the skunk, fox, raccoon and bat are important sources of infection. Globally, the dog is the most important reservoir, particularly in developing countries. In Asia, Africa and Latin America the main reservoir is not wildlife but stray dogs. In these areas, human infection and fatalities are more common. Once symptoms of the disease develop, rabies is nearly always fatal. The disease may be suspected based on clinical signs, but laboratory tests are required to confirm the diagnosis. Rabies is caused by a single-stranded RNA virus Lyssaviruses in the Rhabdovirus family. To date, over 15 different Lyssaviruses have been described. Rabies virus is the most important member of the genus. Rabies virus affects the central nervous system of warmblooded animals, including humans. The disease can have a long incubation period (six months and more) and symptoms may take several weeks to appear after infection. Once symptoms appear, rabies is always fatal. Rabies is a disease listed in the World Organization for Animal Health (OIE) Terrestrial Animal Health Code and must be reported to the OIE (OIE Terrestrial Animal Health Code).

TRANSMISSION AND PATHOGENESIS

Transmission almost always occurs via introduction of virus-laden saliva into tissues, usually by the bite of a rabid animal. Virus from saliva, salivary glands, or brain can cause infection by entering the body through fresh wounds or intact mucous membranes. Saliva is infectious at the time clinical signs occur, but domestic dogs, cats, and ferrets may shed virus for several days before onset of clinical signs. Rabies virus is highly neurotropic. After the virus enters the dog's body, it replicates in the cells of the muscles. Then virus spreads to the nearest nerve fibers, including all peripheral, sensory and motor nerves, traveling from there to the CNS. The virus travels via the peripheral nerves to the spinal cord and ascends to the brain. After reaching the brain, the virus travels via peripheral nerves to the salivary glands. If an animal is capable of transmitting rabies via its saliva, virus will be detectable in the brain.Virus is shed intermittently in the saliva. Haematogenous spread does not occur. Near the end of the clinical phase, after replication in the CNS, virus may be found in nearly every innervated organ.

The incubation period varies from several days to several months. The virus usually incubates from two to eight weeks before signs are noticed. Typically, the virus remains at the inoculation site for a considerable time. Most rabies cases in dogs develop within 21–80 days after exposure, but the incubation period may be shorter or considerably longer. Transmission of the virus through saliva can happen as early as ten days before symptoms appear. Once symptoms are present, the disease is fatal for both animals and humans.

CLINICAL SIGNS

Rabies virus causes acute encephalitis in all warmblooded hosts. In dogs, the first symptoms of rabies may be nonspecific and include lethargy, fever, vomiting, and anorexia. All animals exhibit certain neurological signs as a result of rabies. Clinical signs of rabies will vary depending on the effect of the virus on the brain. Signs progress within days to cerebral dysfunction, cranial nerve dysfunction, ataxia, weakness, paralysis, seizures, difficulty breathing, difficulty swallowing, excessive salivation, abnormal behaviour, aggression, and/or self-mutilation. Typical signs include sudden behavioural changes and progressive paralysis leading to death. It is important to understand that animal may die rapidly without demonstrating significant clinical signs. The most reliable signs, regardless of species, are acute behavioural changes and unexplained progressive paralysis. Behavioural changes may include sudden anorexia, signs of apprehension or nervousness, irritability, and hyperexcitability. The animal may seek solitude. Ataxia, altered phonation, and changes in temperament are apparent. Uncharacteristic aggression may develop and infected animal may suddenly become vicious.

THE DISEASE PROGRESSES IN FEW STAGES

Prodromal form. In the first or prodromal phase the dog undergoes a change in temperament and behaviour. Early, the dog can show only mild signs of CNS abnormalities. Fever may be present. Quiet dogs become agitated and active pets become nervous or shy. Pruritus may be present at the site of exposure. This first stage usually lasts for about 1-3 days. Most dogs will then progress to the paralytic stage, the furious stage, or a combination of the two. As said earlier, some dogs will have infection without displaying any major symptoms.

Paralytic (dumb) form. The majority of canine cases will show paralytic (dumb) phase. Animals with this form of rabies may be depressed or unusually docile. This stage is characterized by the inability to swallow, distortion of the face leading to a typical sign of foaming saliva around the mouth. This is manifest by ataxia and paralysis of the throat and masseter muscles, often with profuse

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* This paper was presented at the FECAVA symposium on rabies held in Barcelona on 16 October 2015. Eur J Comp An Pract, Spring 2016; (26)1: p10-p14 Go to http://www.ejcap.org for the interactive online presentation of this paper

salivation and the inability to swallow. Dropping of the lower jaw is common in dogs. Voice or bark changes are often noticed. Some animals may develop paralysis beginning at the hind extremities with typical signs of lower motor neuron paralysis. Disorientation, incoordination and staggering may occur, caused by paralysis of the hind legs. Eventually, complete paralysis and coma are followed by death. Owners will frequently think the dog has something stuck in the mouth or throat. Care should be taken in examination since rabies is transmitted by saliva. This form lasts 1 to 7 days, from onset of overt signs to death.

Excitative (furious) form. The prodromal stage is followed by a period of severe agitation and aggressiveness. Initially, a dog that has become infected may show extreme behavioural changes such as restlessness or apprehension and aggression. Furious rabies is characterized by extreme behavioural changes, including overt aggression and attack behaviour. Animals with this form of rabies may demonstrate sudden behaviour changes, and attack without provocation. Animals may be anxious, highly excitable and/or aggressive with intermittent periods of depression. A fever may also be present at this stage. As the virus progresses, an infected dog may become hypersensitive to touch, light and sound. The animal often bites any material. Rabid dog becomes highly excitable and displays evidence of a depraved appetite, eating and chewing stones, earth and rubbish (pica).

Infected dogs may develop a typical high barking sound during furious rabies. As the disease progresses, muscular weakness, incoordination and seizures are common.

Paralysis eventually sets in and the rabid animal may be unable to eat and drink. Hydrophobia (fear of water) is not a sign of rabies in dogs. This is a feature of human rabies. Death results from progressive paralysis. Death may follow convulsions even without the paralytic stage of the disease. This form lasts 2 to 8 days, from onset of overt signs to death.

DIAGNOSIS

Clinical diagnosis is difficult, especially in areas where rabies is uncommon. In the early stages, rabies can easily be confused with other diseases or with normal aggressive tendencies. Differential diagnosis that should be included in case of suspected rabies include: encephalitis: viral (canine distemper), immune mediated, pseudorabies, toxicity (e.g. lead), portosystemic shunt, hypoglycemia, neoplasia, trauma, other causes of ptyalism.

When rabies is suspected and definitive diagnosis is required, laboratory confirmation is indicated. Suspect animals should be euthanized, and the head removed for laboratory shipment. Rabies diagnosis should be done by a qualified laboratory, designated by the local or state health department in accordance with established standardized national protocols for rabies testing. Immunofluorescence microscopy on fresh brain tissue, which allows direct visual observation of a specific antigen-antibody reaction, is the current test of choice. It can establish a highly specific diagnosis within a few hours. Brain tissues examined must include medulla oblongata and cerebellum (and should be preserved by refrigeration with wet ice or cold packs). Virus isolation by the mouse inoculation test or tissue culture techniques using mouse neuroblastoma cells may be used for confirmation of indeterminate fluorescent antibody results.

PREVENTION AND CONTROL

Rabies is a vaccine-preventable disease. The most costeffective strategy for preventing rabies in people is by eliminating rabies in dogs through vaccination. Integrated veterinary management of local animal populations, by mass vaccination of dogs and community promotion of responsible pet ownership, is the most cost-effective, humane, long-term solution toward eliminating regional canine rabies in a One Health context.

Comprehensive guidelines for control in dogs have been prepared internationally by the World Health Organization and they include the following:

1. notification of suspected cases, and euthanasia of dogs with clinical signs and dogs bitten by a suspected rabid animal;
2. reduction of contact rates between susceptible dogs by leash laws, dog movement control, and quarantine;
3. mass immunization of dogs by campaigns and by continuing vaccination of young dogs;
4. stray dog control and euthanasia of unvaccinated dogs with low levels of dependency on, or restriction by, people; and
5. dog registration.

Many effective vaccines, such as modified-live virus, recombinant, and inactivated types, are available for use throughout the world. Recommended vaccination frequency varies from 1 to 3 years, after an initial series of two vaccines 1 year apart.

ZOONOTIC ASPECT

Rabies has the highest case fatality of any infectious disease. When a person is exposed to an animal suspected of having rabies, the risk of rabies virus transmission should be evaluated carefully. Risk assessment should include consideration of the species of animal involved, the prevalence of rabies in the area, whether exposure sufficient to transmit rabies virus occurred, and the current status of the animal and its availability for diagnostic testing. Any healthy domestic dog whether vaccinated against rabies or not, that exposes (bites or deposits saliva in a fresh wound or on a mucous membrane) a person should be confined for 10 days; if the animal develops any signs of rabies during that period, it should be euthanized and its brain promptly submitted for rabies diagnosis. If the dog responsible for the exposure is stray or unwanted, it may be euthanized as soon as possible and submitted for rabies diagnosis. Since the advent of testing by immunofluorescence microscopy, there is no value in holding such animals to “let the disease progress” as an aid to diagnosis.

Internationally, the World Health Organization recommends several types of cell-culture vaccines for human groups at risk. Occupational groups regularly in contact with animals for

example, veterinarians, animal control and wildlife officers should obtain protection through pre-exposure vaccination. Abattoir personnel, particularly in endemic areas, must take preventive actions to prevent infection from saliva, salivary gland and nervous tissue of infected animals. Infection does not occur by consumption of meat from a rabid animal. Preexposure immunization is strongly recommended for people in high-risk groups. Preexposure vaccine is administered on days 0, 7, and 21 or 28. Preexposure prophylaxis alone cannot be relied on in the event of subsequent rabies virus exposure and must be supplemented by a limited postexposure regimen (two doses of vaccine, IM, on days 0 and 3). For healthy, unvaccinated patients bitten by a rabid animal, postexposure prophylaxis consists of wound care, local infiltration of rabies immune globulin, and vaccine administration on days 0, 3, 7, and 14. Modern postexposure prophylaxis assures human survival if it is provided on time and in appropriate manner.

Clinical cases: not always obvious

Clinical diagnosis is difficult, especially in areas where rabies is uncommon. In the early stages, rabies can easily be confused with other diseases or with normal aggressive tendencies, as shown by these two cases seen by the author (Serbia, early 2000s).

Clinical case n° 1

Muna, a 3-year-old intact female GSD. Owned by a breeder, living in the countryside and kennelled since puppyhood. Used as a show dog.

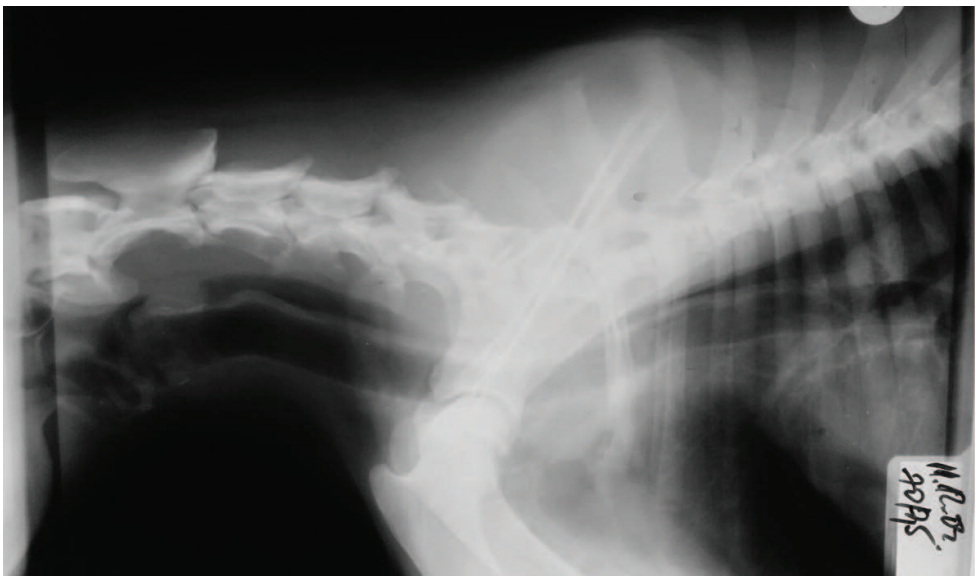
Presenting history

Retching, scratching neck region, very mild salivation, subtle weakness. As the dog had been fed raw fish heads, the owner was suspicious of a foreign body in the mouth/throat. The dog had been seen by a local vet, who also suspected a foreign body in the mouth. The vet had sedated the dog (ketamine only) and had explored the mouth (without gloves). Antibiotics and steroids were prescribed 'just in case' and the dog was referred for X-rays at the owner's request.

Clinical examination

T 39.5°C. Chest auscultation was unremarkable, as was abdominal palpation. Muna showed moderate salivation, muscle twitching, vocalisation, anisocoria and was semi-recumbent – some of which could also be attributed by ketamine. However, they could also be caused by rabies, which is why quarantine and observation was recommended, in particular since there was no history of rabies vaccination. However, the owner refused to leave the dog in observation and spent the night with the dog. The local veterinary inspector and head of infectious department were contacted.

The following morning, the dog showed moderate salivation, mild ataxia when walking and muscle twitching. The dog also seemed somewhat 'disorientated'. The owner insisted on further investigation to rule out the foreign body, so an X-ray was taken. Chest radiographs showed no foreign body – but gas in the oesophagus, which is consistent with paralysis of the throat and masseter muscles.



X-ray of Muna, showing gas in the oesophagus.

Follow-up

No underlying disease could be found, nor any history of exposure to rabies. The owner had become very emotional at the mere suggestion of rabies and refused quarantine and came to remove the dog. As it was physically impossible to retain the dog against the owner's will, the vet convinced the owner to a minimum agreement of placing it in isolation (kennel) at all times for observation, and to contact the vet if the dog died. The referring local vet was also informed.

No news was received for two days. On the third day, the owner called to say that the dog had died ... the previous day ... and had been buried! Despite winter conditions (frozen soil), the body was dug up and was sent to the Serbian Pasteur Institute (EU reference laboratory for rabies). The following day, rabies was confirmed.

Epilogue

As there was a theoretical risk of exposure due to contact with saliva in a fresh open wound, the veterinary staff all underwent post-exposure prophylaxis (five injections of hyperimmune antiserum over 28 days).

Clinical case n° 2

Presenting history

A 2-year-old female German short-haired pointer, used as a hunting dog, was referred by a local veterinarian for hind limb weakness for two days. Steroids had been prescribed but no improvement was seen.

Clinical examination

As rabies was part of the differential diagnosis, the clinical examination consisted of observation only. The dog was ataxic, but also showed moderate salivation, muscle twitching and a lowered mandible. The dog also seemed anxious, disoriented and was highly excitable. The dog was referred to a veterinary school for isolation and observation.

Follow-up

The dog died three days later. Rabies was confirmed.

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