On skunk rabies and its prevention in North America

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Abstract

The case report by Navarro-Lopez et al., (2023) in this issue describes a thorough differential diagnosis in an equine with acute neurological disease. Rabies was confirmed by direct fluorescent antibody test (DFA). Rabies virus (RABV) was isolated from brain tissue of the ill mare by intracerebral inoculation in sucking mice. Sequencing and phylogenetic inference allowed the identification of the rabies virus variant (RVV) associated with this case. Thus, Navarro-Lopez et al., reported that the rabid mare got infected with a rabies virus variant associated with skunks. This clinical commentary elaborates on the seemingly rare skunk rabies across North America (NA) highlighting its relevance in human and animal health that have remained somehow neglected

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The case report by Navarro-Lopez et al., (2023) in this issue describes a thorough differential diagnosis in an equine with acute neurological disease. Rabies was confirmed by direct fluorescent antibody test (DFA). Rabies virus (RABV) was isolated from brain tissue of the ill mare by intracerebral inoculation in sucking mice. Sequencing and phylogenetic inference allowed the identification of the rabies virus variant (RVV) associated with this case. Thus, Navarro-Lopez et al., reported that the rabid mare got infected with a rabies virus variant associated with skunks. This clinical commentary elaborates on the seemingly rare skunk rabies across North America (NA) highlighting its relevance in human and animal health that have remained somehow neglected.

Over the last two centuries, skunks have been one of the most common wildlife rabid animals across NA (Gremillion-Smith et al., 1988; Ma et al., 2023; Oertli et al., 2009). Early reports of skunk rabies transmitted to humans, companion animals, and farm animals, date from 1826 in lower California (Johnson 1971), where most exposures were associated with spotted skunks (*Spilogale spp*). Skunk rabies across the Central Great Plains mainly involving striped skunks (*Mephitis mephitis*) began to be observed during the second half of the 19th century (Hovey 1874).

Due to advances in molecular epidemiology, phylogenetics and notable improvements on wildlife rabies surveillance (primarily passive both laboratory-based and epidemiological), it is now known that the skunk rabies epizootic is comprised by regional independent enzootics in which RVVs with particular evolutionary histories predominate (Charlton et al., 1988; Clark et al., 2015; Kuzmina et al., 2013). The north-central skunk (NC SK), the California skunk (CA SK), the Baja California Sur Mexico skunk (BCSMX SK), the Northwest Mexico skunk (NWMX SK), and the Yucatan Mexico skunk (YUCMX SK) enzootics, maintain circulation of specific RVVs that originated from long standing dog rabies epizootics prevailing in their respective regions, Figure 1 (Barton et al., 2012; Davis et al., 2013; Kuzmina et al., 2013; Velasco-Villa et al., 2002; 2005; 2008; 2017). Meanwhile, the South-central skunk (SC SK) and the North-central Mexico skunk (NCMX SK) enzootics, maintain RVVs that originated from ancestral bat rabies epizootics, Figure 1 (Barton et al., 2012; Davis et al., 2013; Kuzmina et al., 2013; Velasco-Villa et al., 2002; 2005; 2008; 2017).

Thus far, individuals of all skunk species in NA have been reported to be rabid (*Conepatus leuconotus* , *Conepatus semistriatus* ,*Mephitis mephitis* , *Mephitis macroura* , *Spilogale gracillis* , *Spilogale putorius* , *Spilogale leucoparia* and*Spilogale yucatanensis*), however only *M. mephitis* and some*Spilogale spp* have been recognized as major rabies reservoir hosts across NA (Aranda et al., 1999; Dragoo et al., 2004; 2006; Gremillion-Smith et al., 1988; Oertli et al., 2009; Velasco-Villa et al., 2002; 2005).

Albeit their divergent origins, all RVVs circulating in NA skunk populations seem to be virulent and capable of causing rabies in any sympatric mammal a rabid skunk may encounter (Barton et al., 2012; Charlton et al., 1991; Hill et al., 1993). Rabies is a highly lethal infectious disease for all mammals including the rabies reservoir hosts – *i.e* ., mammal species in the Carnivore and Chiroptera orders that play a central role in maintaining specific RVVs through intraspecific transmission (Smith 1989). The most common mechanism of rabies transmission is by direct contact through bites of sick animals infected with RABV. However, rabies could be acquired through contact with RABV infected/contaminated saliva or brain tissue from a rabid animal in open wounds or mucosa (Fisher et al., 2018). The incubation period for rabies in skunks varies from 21 to 117 days, which is similar to that observed in most mammals (Gremillion-Smith et al., 1988; Oertli et al., 2009; Borchering et al., 2012). A rabid skunk may stay alive for up to 10 days after the onset of neurological signs (Charlton et al., 1987). However, RABV shedding in saliva can occur up to 6 days before the onset of neurological signs (Charlton et al., 1991), thereby, any skunk bite should be considered as a rabies exposure, particularly if the animal is not available for laboratory diagnosis. The most common rabies signs in rabid skunks are abnormal behavior (active during daytime), hyperesthesia, hypersensitiveness to light noise or movement, incoordination, and extremely aggressive behavior (Gremillion-Smith et al., 1988; Oertli et al., 2009). Rabid skunk attacks on people or animals have been reported as incursions at animal enclosures, people's homes and/or camping sites (Johnson 1971; Hovey 1874; Gremillion-Smith et al., 1988; Oertli et al., 2009).

Skunk rabies occurs throughout the year with disease peaks during spring, when males increase their regular home range for mating. Skunk rabies epizootic cycles have been reported to occur every 4, 6, 8 or 20 years in the U. S. and Canada, depending on the region or the period of observation (Charlton et al., 1991; Gremillion-Smith et al., 1988; Oertli et al., 2009; Pybus 1988).

Understanding the current geographic distribution of rabies enzootics and the main reservoir host species associated with them allows for a better design of species targeted control, prevention, and elimination strategies, as well as for tailored outreach campaigns aimed at the most vulnerable populations (Fehlner-Gardiner et al., 2018; Pepin et al., 2017; Wohlers et al., 2018). Striped skunks (*M mephitis*) are considered generalist, while other species such as *Conepatus spp and Spilogale spp* could be more specialized inhabiting diverse ecosystems, comprising high forests to plains and semi-desertic regions, including transition areas. Unlike most skunk species, striped skunks have successfully adapted across the urbanization gradient, including densely populated areas (Harrington et al., 2017; Hass and Dragoo 2017; Ramey et al., 2013). Skunks may be targeted for removal or exclusion, due to the nuisance provoked by their pungent defense scent and the occasional damage they cause to people properties or crops (Harrington et al., 2018). In some instances, skunks may be removed through poisoning or trapping. The latter is not considered practical, nor cost effective or feasible in rural and farm areas (Harrington et al., 2018). Skunk extermination or extirpation from certain areas often leads to ecological imbalances and the emergence of pests, namely rodents and some insects they predate on (Harrington et al., 2018; Hass and Dragoo 2017). Measures that combine oral rabies vaccination and humane population control (such as hormone derived contraception or relocation measures) may be more acceptable and effective to mitigate rabies exposures to humans, companion and farm animals (Charlton et al., 1992; Elmore et al., 2017; Feldhamer et al., 2003; Richards et al., 2019).

Skunk rabies rarely affects humans in the U. S. and Canada, with only few cases reported in Mexico in the last three decades (Aranda et al., 1999; Arechiga-Ceballos et al., 2022). Securing camping tent's entrances and/or keeping doors closed at homes and stables may help prevent incursions of rabid skunks (Gremillion-Smith et al., 1988; Hovey 1874; Johnson 1971; Oertli et al., 2009). There is no accurate estimation of the total number of rabies cases due to skunk RVVs or rabid skunk exposures in domesticated and wildlife animals throughout NA (Ma et al., 2023). Nonetheless, it would be recommended to be cautious of its presence at regions known enzootic for skunk rabies (Fehlner-Gardiner et al., 2018;). Economic losses due to skunk rabies in farm animals have not been accurately estimated, but the loss of high-value breeders, racehorses, or other farm animals due to skunk rabies have been reported (Aranda et al., 1999; Arechiga-Ceballos et al., 2022; Velasco-Villa et al 2002). Commonly available parenteral rabies vaccines labeled for use in cattle, horses, and other farm animals, protect against all known RVVs, including those present in rabid skunks (Green et al., 2011; Wohlers et al., 2018). However, having pre-exposure vaccination (receiving vaccine before an exposure to rabies occurs), both humans and animals does not always warrant 100% immunity after severe exposure to a confirmed rabid animal (Larghi 2004; National Association of State Public Health Veterinarians Committee 2008). If the viral entry location (bites) is too close to the head or the spine, and a high RABV load has been delivered by a rabid animal, RABV could potentially reach the central nervous system (CNS) before the immune system can stop infection at the periphery (Brunt et al., 2021; Green t al., 2011). Once RABV reaches the CNS, rabies will be almost 100% fatal, thereby it is highly recommended to consult a veterinarian or a rabies medical expert to help assess exposure levels and decide the pertinence to provide booster vaccinations (Green et al., 2011; National Association of State Public Health Veterinarians Committee 2008; Rupprecht et al., 2006).

Currently, there are no systematic oral vaccination campaigns to reduce or eliminate the skunk rabies epizootic in NA (Elmore et al., 2017). However, some efforts have been conducted in the U. S and Canada to reduce or mitigate the associated risks that imply the expansion of skunk rabies outbreaks, or the establishment of new RVVs in certain skunk populations (Elmore et al., 2017; Fehlner-Gardiner et al., 2012; Slate et al., 2005). Examples of outbreaks and the detection of none skunk-associated RVVs in skunks include a skunk rabies outbreak in Flagstaff Arizona, where skunk to skunk rabies transmission of a RVV maintained by big brown bats lasted over consecutive years; and southern Canada where intraspecific rabies transmission of the raccoon RVV in skunk populations sparked a rabies outbreak among skunks (Elmore et al., 2017).

Since skunks seem to have remarkable ecological plasticity and an outstanding susceptibility to RABV from different origins, it would not be surprising if new skunk rabies enzootic cycles appear (Elmore et al., 2017; Fehlner-Gardiner et al., 2012; Slate et al., 2005). Rabies vaccination should be considered to mitigate the effects of skunk transmitted rabies in horses and all other rabies susceptible farm animals when pertinent (Green et al., 2011; National Association of State Public Health Veterinarians Committee 2008; Rupprecht et al., 2006). Feasibility of oral rabies vaccination for skunks continues to be explored, and ongoing research efforts include improvement of the uptake (such as improved vaccine baits that could be more attractive for skunk consumption), as well as formulations that evaluate different vectors, and genetically modified RABVs and their concentrations (Elmore et al., 2017; Fehlner-Gardiner et al., 2012; Slate et al., 2005).

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