SCIENTIFIC LITERATURE

CASE REPORT

Case Study: Rabies Vaccine Adverse Reaction in a Dog

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A B S T R A C T

An apparently healthy adult, neutered male Great Dane was given a legally mandated rabies vaccine booster. This was the dog's third rabies booster, although the vaccine used this time contained thimerosal (mercury). For the next few days, the dog was febrile, irritable and anorexic. By a week later (post-vaccination day 10), the dog was lethargic and had developed ulcerating sores along the face, chest, back and abdomen. Therapy was initiated for ischemic post-rabies panniculitis, which allowed for a gradual recovery over the next 2 months. The dog received a medical exemption from future rabies virus boosters, and was never vaccinated again. This case illustrates the potential for adverse vaccine reactions even in large breed adult dogs. A review of the literature on rabies exposure risk, adverse vaccine events (vaccinosis), and their management and treatment is provided.

Abbreviations

AE: Adverse Events; ASIA: Autoimmune Syndrome Induced by Adjuvants; CNS: Central Nervous System; CVB: Center for Veterinary Biologics; IMHA: Immune-Mediated Hemolytic Anemia; IMTP: Immune-Mediated Thrombocytopenia; TNF-alpha: Tumor Necrosis Factor-alpha; USDA: United States Department of Agriculture

Introduction

There have been no documented cases of rabies in North America in vaccinated, immunized dogs and cats for two decades, although the disease still exists among wild life and feral companion animals [1]. This is presumably due to the fact that, for decades, companion and livestock animals have been vaccinated routinely and repeatedly to protect them from rabies and the other common serious infectious viral and bacterial diseases with few reported Adverse Events (AE) [1-4]. But, veterinarians still need to heed the potential for AE and determine what constitutes "acceptable harm" [1-3].

Killed, inactivated vaccines, like those for rabies, contain potent immunologic adjuvants which act to accelerate, prolong, or enhance antigen-specific immune responses when used together with specific vaccine antigens [5,6]. These adjuvants are incorporated into vaccines to enhance their

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immunogenicity, but this also increases the risk of autoimmune and inflammatory AE following vaccination [5].

Case Study

The patient was a 5-year-old neutered male, black and white Great Dane; the dog was apparently healthy when presented to the client's regular veterinary clinic for a routine health examination and vaccination update. The caregiver had received a card in the mail from the clinic reminding her that the dog was due for the legally mandated 3-year rabies booster. The other routine "core" vaccines (distemper, adenovirus-2 and parvovirus), also scheduled on a three-year program [4], were not due for another year.

As this dog seemed very healthy when examined at the veterinary clinic for the rabies booster, the dog was given a 3-year licensed canine rabies vaccine that also contained thimerosal (mercury) as a preservative [7]. The vaccine was given intramuscularly above the left shoulder. While this was the dog's third rabies booster and the two prior vaccines were thimerosal-free and had not elicited any AE, he became febrile, irritable and was anorexic for several days afterwards. There were no other known inciting cause or events identified.

About a week later (post-vaccination day 10), however, the dog was lethargic and had developed similar ulcerating sores along the face, chest, back, hind legs and abdomen (Figure 1). The dog was rushed to the veterinary clinic, where treatment was initiated for ischemic post-rabies panniculitis (defined as localized ischemic skin disease associated with a rabies vaccination site and a temporal link with the vaccination) [8,9].

The attending veterinarian prescribed the combination therapy believed to be beneficial in such cases [9]:

Omega-3 and omega-6 fatty acid supplementation was given at the standard 3:1 ratio for dogs and a dose of 40 mg/kg/day; vitamin E (800-1000 IU/day), and pentoxifylline at 20 mg/kg/day. The latter drug is a methylxanthine derivative that has rheological and immune modulatory effects, increases red blood cell deformability, alters tissue response to many inflammatory cytokines, and diminishes production of TNF-alpha.

The use of topical corticosteroids for the anti-inflammatoy treatment of ischemic dermatopathy is controversial, and so caution is advised to avoid overdosing or sustained use. Further, potent topical corticosteroids may diminish epidermal thickness leading to increased skin fragility [9].

The dog was successfully treated for vaccinosis with tapering doses of the prescribed drugs given over 6 weeks. The patient was also given the oral homeopathic remedies, Thuja and Lyssin at 30 c potency, for several days to help detoxify his rabies miasm [1,10]. Since then, he has received a permanent medical exemption from future rabies virus vaccine boosters, and was never vaccinated again.

Figure 1: The initial skin lesions exhibit small alopecic macules or plaques that develop at the injection site of a prior rabies vaccine.

Discussion

The clinical case described here illustrates several factors that contribute to the risk of AE following vaccination, namely [1-15]: genetic predisposition (family history and breed type), influence of sex

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hormonal change (estrus), and type of vaccine and adjuvant used (rabies and thimerosal). Killed, inactivated vaccines make up about 15% of veterinary biologicals used in companion animals, wildlife and livestock species. However, importantly, they have been associated with 85% of the post-vaccination AE, mainly because of the acute and sub-acute AE induced by the adjuvants [1,5,8-11,13]. Furthermore, documented AE from the adjuvants used in human vaccines, especially those containing aluminum and thimerosal (a mercury salt), continue to appear in the literature [1,6,7].

Simultaneous administration of even two or three vaccine adjuvants can overcome genetic resistance to autoimmunity as documented in experimental studies [1,6]. Clinical experience has shown that children are more vulnerable to vaccine toxicity than adults; and they are routinely exposed to more vaccine adjuvants than adults. The same situation pertains to companion pet animals, which readers familiar with the human vaccine literature and experience may not realize. Adjuvants impact the Central Nervous System (CNS) at all levels, primarily by changing gene expression biomarkers [1,6,7]. Also, it is now recognized that the neuro-immune axis, heavily targeted by aluminum and mercury adjuvants, plays a vital role in brain development and immune function [1]. Animal model and human clinical studies have shown that these metals can cause what is defined since 2011 as the Autoimmune Syndrome Induced by Adjuvants (ASIA syndrome) [1,6,7].

The type of allergy induced by metals is a delayed-type hypersensitivity and manifests often as a contact or superficial ischemic panniculitis as exhibited by the case reported here [1,8,9]. These metals exert both specific and non-specific effects that contribute to the ASIA syndrome [7].

Post-vaccinal polyneuropathy is a recognized entity associated occasionally with the use mostly of canine distemper and rabies vaccines, but any vaccine could presumably be implicated [7,11]. This can result in various clinical signs including muscular atrophy, inhibition or interruption of neuronal control of tissue and organ function, muscular excitation, incoordination and weakness, as well as seizures [1,2,10].

Certain breeds or families of dogs appear to be more susceptible to AE, and particularly exhibit post-vaccinal seizures, high fevers, and painful episodes of masticatory myositis and hypertrophic osteodystrophy [1,2,9,10]. Toy and smaller dogs, as well as those with white or lighter coat color appear to be at increased risk for AE [2,9,15]. The patient of this report was a black and white Great Dane, a coat color that along with the Harlequin variety of this breed, has been associated with more AE not only from vaccines but also from other chemical exposures (e.g. herbicides, pesticides, fertilizers), drugs (e.g. sulfonamides) and preventives given for heartworm, flea and tick control. At the time of the rabies vaccination AE reported here, however, none of these other exposures was involved. Age and sex predilections have not been documented [2,4,9]. Other clinical signs include: stiffness, sore joints and abdominal tenderness, susceptibility to infections, chronic digestive problems, neurological disorders and encephalitis, behavioral aggression and separation anxiety, destruction and shredding of clothing and bedding, obsessive behavior, barking, fearfulness, self-mutilation, tail chewing, pica with eating wood, stones, earth, and feces, and fibrosarcomas at the vaccine injection site. Severe AE also can exhibit as patient collapse with auto-agglutinated red blood cells and icterus (Immune-Mediated Hemolytic Anemia, IMHA), or generalized petechiae and ecchymotic hemorrhages (Immune-Mediated Thrombocytopenia, IMTP). Hepatic enzymes may be markedly elevated, and liver or kidney failure may occur by itself or accompany bone marrow suppression.

Post-rabies vaccination-associated AE has been attributed to an idiosyncratic immunologic reaction to rabies antigen that partially targets blood vessels. Rabies viral antigen has been documented in the walls of dermal blood vessels and in the epithelium of hair follicles [9]. The initial skin lesions exhibit small alopecic macules or plaques that develop at the injection site of a prior rabies vaccine (as shown in Figure 1). The time between vaccination and noticing the lesion usually is between one and six months. Since this syndrome is seen predominantly in small dogs, one can speculate that the

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disease is linked to the increased antigenic load given to these smaller dogs, since the same volume of rabies vaccine is given to all dogs [1, 9].

With these factors in mind, we should advise companion animal breeders and caregivers of the potential for genetically susceptible littermates and relatives to be at increased risk for similar AE [2,14,15]. In popular (or rare) inbred and line bred animals, the breed in general can be at increased risk, because of the genetic predisposition that promotes an adverse response to viral or other infectious agent challenge [14,15]. The recently weaned young puppy or kitten being placed in a new environment may be at particular risk. Furthermore, some veterinarians advocate giving vaccines once a week in perceived or legitimate high exposure risk situations; such practice has no scientific basis and clearly can be harmful [2-4].

When an adequate immune memory has already been established by measuring serum vaccine-induced immunity (titer) levels, it is unwise and can be unsafe to introduce unnecessary antigen, adjuvant, and preservatives by administering booster vaccines [2-4]. By measuring serum antibody titers triennially or more often, if needed, one can assess whether a given animal's humoral immune response has fallen below levels of adequate immune memory. In that event, an appropriate vaccine booster can be administered (4).

Rabies vaccines are the most common group of biological products identified in adverse event reports received by the USDA's Center for Veterinary Biologics (CVB) [11]. Currently, 14 rabies vaccines are labeled for use in dogs, and all but two of them contain thimerosal (mercury) as a preservative (1). While all rabies vaccines are evaluated for safety prior to licensure, these studies may not detect every safety concern for a number of reasons: insufficient number of animals for low frequency events, insufficient duration of observation, sensitivities of subpopulations (e.g., breed, reproductive status, and unintended species), or interactions with concomitantly administered products [1,11].

Despite the serious under-reporting of vaccine-induced AE, the 2008 report from the USDA's CVB states that between April 1, 2004 and March 31, 2007, nearly 10,000 adverse event reports (all animal species) were received by manufacturers of rabies vaccines [11]. Approximately 65% of the manufacturer's reports involved dogs. During the 3-year period covered in this report, the CVB received 246 adverse event reports for dogs in which a rabies vaccine was identified as one of the products administered [11].

Conclusion

Where appropriate, we must standardize and individualize vaccination policies to ensure the safety and efficacy of human and veterinary vaccines [1,4,6,12,14]. Despite this logical recommendation, there remains controversy, failure to comply with current national vaccine policies and guidelines [4], resistance to change, and denial of adverse events within the human health and veterinary communities as well as within society as a whole [1,6,14,15].

References

1. Dodds WJ. (2016). Rabies virus protection issues and therapy. Global Vaccines Immunol 1: 51-54.

2. Dodds WJ. (1999). More bumps on the vaccine road. Adv Vet Med. 41: 715-732.

3. Tizard I. (1990). Risks associated with use of live vaccines. J Am Vet Med Assoc. 196: 1851-1858.

4. Welborn LV, DeVries JG, Ford R, Franklin RT, Hurley KF, et al. (2011). American Animal Hospital Association (AAHA) Canine Vaccination Task Force, 2011 AAHA canine vaccination guidelines. J Am Anim Hosp Assoc. 47: 1-42.

5. Spickler AR, Roth JA. (2003). Adjuvants in veterinary vaccines: modes of action and adverse effects. J Vet Intern Med. 17: 273-281.

6. Cruz-Tapias P, Agmon-Levin N, Israeli E, Anaya JM, Shoenfeld Y. (2013). Autoimmune (auto-inflammatory) syndrome induced by adjuvants (ASIA)--animal models as a proof of concept. Curr Med Chem. 20: 4030-4036.

7. Stejskal V. (2013). Mercury-induced inflammation: yet another example of ASIA syndrome. Isr Med Assoc J. 15: 714-715.

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8. Wilcock BP, Yager JA. (1986). Focal cutaneous vasculitis and alopecia at sites of rabies vaccination in dogs. J Am Vet Med Assoc. 188: 1174-1177.

9. Ihrke PJ. (2006). Ischemic skin disease in the dog. Proceedings 31st Congress World Small Animal Veterinary Association 2006, Prague, Czech Republic.

10. Dodds WJ. (2015). Canine seizure disorders and the immune system. Case studies. J Am Hol Vet Med Assoc. 39: 29-31.

11. Frana TS, Clough NE, Gatewood DM, Rupprecht CE. (2008). Post-marketing surveillance of rabies vaccines for dogs to evaluate safety and efficacy. J Am Vet Med Assoc. 232: 1000-1002.

12. Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y. (2009). Adjuvants and autoimmunity. Lupus. 18: 1217-1225.

13. Heegaard PM, Dedieu L, Johnson N, Le Potier MF, Mockey M, et al. (2011). Adjuvants and delivery systems in veterinary vaccinology: current state and future developments. Arch Virol. 156: 183-202.

14. Dodds WJ. (2001). Vaccination protocols for dogs predisposed to vaccine reactions. J Am An Hosp Assoc. 37: 211-4.

15. Dodds WJ. (2002). Complementary and alternative veterinary medicine: the immune system. Clin Tech Small Anim Pract. 17: 58-63.