Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Adverse Reactions to Vaccination

From Anaphylaxis to Autoimmunity

Laurel J. Gershwin, DVM, PhD

KEYWORDS

• Vaccine reactions • IgE • Anaphylaxis • Autoimmunity • Arthus reaction

KEY POINTS

- Vaccines are important for protection of individual animals and for creation of herd immunity against infectious diseases.
- Induction of immune responses to nontarget antigens present in most vaccines can lead to allergic sensitization, particularly in breeds with genetic predisposition.
- Reactions to vaccines can vary from allergic events (face swelling) to anaphylactic shock. Although uncommon, such responses can occur.
- Autoimmune diseases have a variety of causes and generally have a genetic predisposition. Overvaccination in a patient with a predisposition to autoimmune disease may enhance the likelihood for development of an autoimmune response.

Prevention of infectious disease by the use of vaccination is one of the most important procedures performed by veterinarians and human health professionals. In some instances, disease has been completely eradicated or greatly reduced through elicitation of herd immunity. Yet, vaccination is not without risk. A risk of vaccination is associated with misuse, overvaccination, and in a small proportion of the vaccinated population the potential for a potentially fatal allergic reaction exists.

HYPERSENSITIVITY TO VACCINE COMPONENTS

In large and small animal patients administration of a viral vaccine, particularly an inactivated and adjuvanted viral vaccine, can elicit an IgE response to proteins present in the vaccine that are nontarget antigens. These are proteins that are present in the cell culture medium used to grow the virus to be used in the vaccine preparation. If the virus is grown on mammalian cells, the most common nontarget antigens are bovine serum proteins, because of the use of fetal bovine serum in cell growth

The author has nothing to disclose.
Department of Pathology, Microbiology & Immunology, School of Veterinary Medicine, University of California, Davis, Vet Med 3A, One Shields Avenue, Davis, CA 95616, USA
E-mail address: ljgershwin@ucdavis.edu

Vet Clin Small Anim 48 (2018) 279–290
https://doi.org/10.1016/j.cvsm.2017.10.005 **vetsmall.theclinics.com**

medium. Proteins shed from the cells used to grow the virus are another source of antigen. The actual virus that is the target immunogen is rarely the source of the misdirected immune response. When virus is grown in eggs, some of the egg protein can become a nontarget antigen. In addition, stabilizers, such as gelatin, can occasionally become a target of an unwanted immune response. The process of vaccine production varies with the manufacturer and the type of adjuvant used, but in general it is impossible for the viral antigens to be completely purified so that the tissue culture products are completely eliminated from the final product. For most patients, this is not a problem. Even if a small amount of IgG is made against fetal bovine serum proteins, it is usually harmless. However, in the population of patients with atopy (those that readily make IgE responses and are often allergic) elicitation of an IgE response by these nontarget antigens presents a potential problem.

The presence of the nontarget antigens in multiple viral vaccines means that each time a patient receives a vaccine containing the nontarget antigens those same nontarget antigens are available to restimulate the immune response.

Patients with atopy (dogs, horses) respond to nontarget antigens by making not only IgG but also IgE antibodies. These IgE antibodies have a high affinity for receptors on mast cells in the skin and nearby mucous membranes of the intestinal tract and the respiratory tract. IgE stays on these mast cells for months, even after serum IgE levels have waned. When the patient receives an injection of vaccine containing more nontarget antigens they bind to the IgE on mast cells and cause degranulation. This is a typical type I hypersensitivity response, with liberation of preformed mediators, such as histamine, and stimulation of production of arachidonic acid metabolites by the lipoxygenase and cyclooxygenase pathways. The leukotrienes thereby created along with the released histamine cause vasoactive responses, increased capillary permeability, and even smooth muscle contraction (**Fig. 1**). In the horse and the dog these responses have been shown to be associated with adverse clinical responses. In the horse, one may see signs of colic and in severe instances, respiratory distress and circulatory collapse (anaphylactic shock). In the dog, a common early sign is swelling and urticaria of the muzzle area, with systemic anaphylaxis occurring usually after one or more such episodes of vaccine responses.

These reactions can be startling to owners and veterinarians and can create a dilemma, particularly when giving the required rabies vaccine.

In 1983, Frick and Brooks[1] hypothesized that immunization of dogs with atopy for canine distemper and parvoviruse would alter immunoregulation of the IgE response. An inbred atopic dog colony was used to test this hypothesis. Vaccination of puppies before sensitization with grass and weed pollen extracts seemed to enhance production of IgE antibodies to the pollen allergens.[1]

HogenEsch and colleagues[2] studied a group of Beagles to evaluate the effect of vaccination on serum concentrations of total and antigen-specific IgE. A multivalent vaccine (without adjuvant) failed to alter IgE levels but addition of the rabies vaccine or rabies vaccine alone (containing alum adjuvant) caused there to be an increase in IgE reactive with vaccine antigens. The reactivity of the IgE included the nontarget proteins in the tissue culture fluid: bovine serum albumin and fibronectin.

The possibility that immunization with vaccines containing alum adjuvants would increase IgE antibody levels reactive with allergens to which the patient had already been sensitized was examined by Tater and colleagues.[3] Using a colony of Maltese-Beagle crossbred dogs known to be allergic to corn and soy, the investigators monitored IgE levels specific to these allergens before and after immunization with commonly used vaccines (canine distemper/adenovirus/measles, parvovirus, parainfluenza virus and rabies). In a second experiment the effect of aluminum

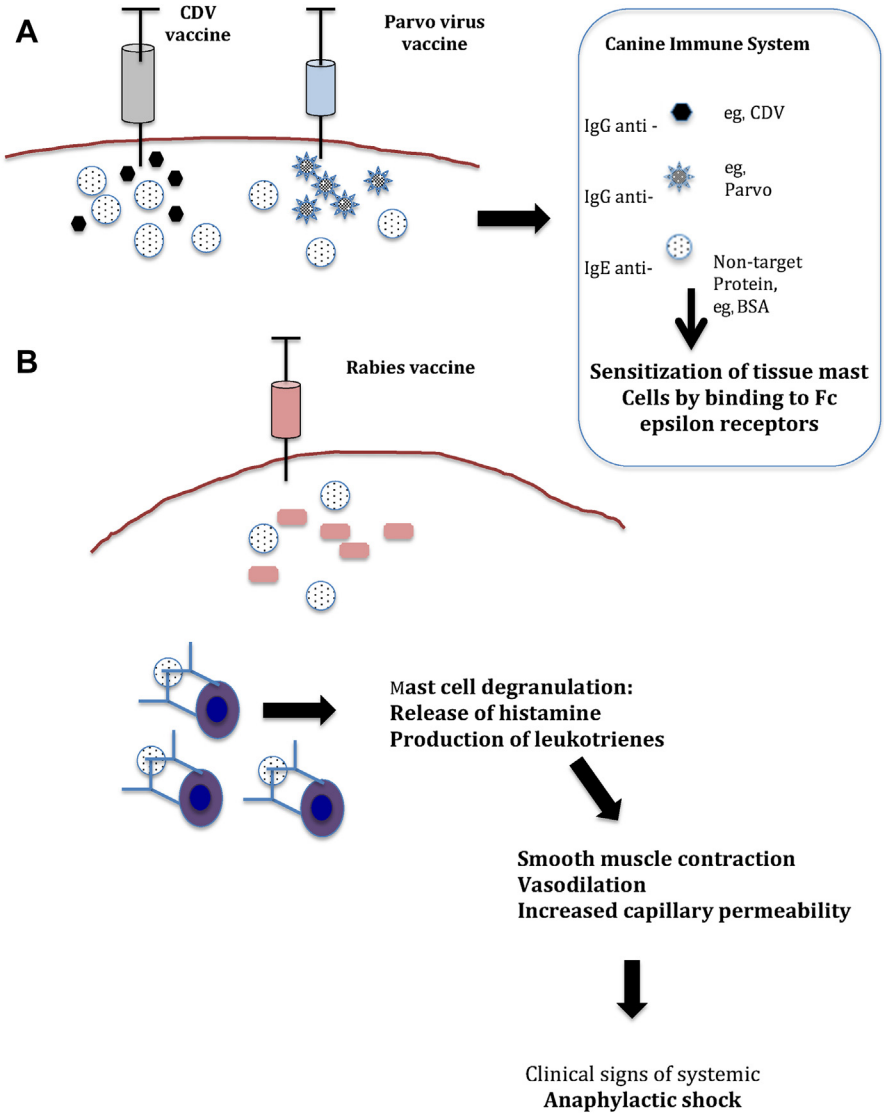

Fig. 1. Viral vaccines contain proteins that are residual from tissue culture media that copurify with virus. These are nontarget antigens. (*A*) Administration of a canine distemper vaccine containing nontarget antigens stimulates the production of antibodies (IgG and sometimes IgE) against the nontarget antigens and against the target viral antigens. The immune response to the nontarget antigens is restimulated by any other vaccine containing these antigens, such as Parvovirus vaccine. (*B*) After initiation of an IgE response to nontarget antigens these antibodies bind tightly to tissue mast cells by their Fc receptors. When another vaccine containing nontarget antigens is given, the IgE molecules bind the antigens, cross-linking the Fc receptors, and trigger degranulation of the mast cells. The release of vasoactive mediators, such as histamine, and the initiation of production of the arachidonic acid mediators, prostaglandins and leukotrienes, causes physiologic effects that result in signs of type I hypersensitivity, which may vary from local facial swelling to anaphylactic shock. BSA, bovine serum albumin; CDV, canine distemper vaccine.

hydroxide adjuvant alone on these same parameters was examined. The study concluded that although increases in total IgE were not observed, the vaccination of dogs with these standard vaccines did cause a significant increase in the levels of IgE specific for the corn and soy allergens to which the dogs had been previously sensitized. Inoculation with alum adjuvant alone did not stimulate the specific IgE response.[3] From this study, one can conclude that vaccination of dogs with concurrent allergy may result in worsening of the allergic condition.

A later study by Ohmori and colleagues[4] examined serum from dogs that had reacted adversely to vaccines with clinical signs relevant to anaphylaxis (collapse, facial edema, dyspnea, and vomiting within 1 hour after vaccination). They compared these sera with sera from dogs that did not develop vaccine reactions. The results showed significantly higher IgE levels in dogs that had reacted adversely. Moreover, the IgE reactivity was directed to proteins in fetal bovine serum and to gelatin and casein used as stabilizers.

Our group followed 77 horses for a period of 5 years to determine if yearly vaccination for West Nile virus would induce IgE responses. High, moderate, and non-IgE responders were identified. The reactivity of the IgE was directed predominantly toward nontarget antigens present in the vaccine, horses with the highest levels of IgE reacted to bovine serum albumin, on antigen-specific enzyme-linked immunosorbent assay and by intradermal skin testing.[5] In a subsequent study, we showed that administration of oligodeoxynucleotides containing CpG motifs concurrently with West Nile virus vaccine in high-responder horses increased the numbers of T regulatory cells and concurrently decreased the IgE response; thus, demonstrating a potential strategy for safer immunization of the high-IgE-responder horse.[6]

Adverse reactions to nontarget antigens have also been observed in human patients. In one study of human children in Sri Lanka high levels of IgE specific to bovine serum albumin were detected in those with measles vaccine allergy.[7] Other reports describe mumps-measles-rubella and/or influenza vaccine reactions in patients with egg allergy caused by growth of the target virus in eggs and the incorporation of ovalbumin in the vaccine as a nontarget antigen.[8] Overall the incidence of vaccine reactions in human patients with egg allergy is low.

TESTING FOR POTENTIAL VACCINE REACTIVITY

The requirement for rabies vaccination is problematic for owners of dogs that have shown allergic reactivity to vaccines. Requirements vary by state and the substitution of a serum antibody titer against rabies virus may be acceptable. One possible method to determine if a vaccine is likely to elicit an adverse (IgE mediated) response is to perform an intradermal skin test using the vaccine. This simple test may allow the veterinarian to select a product that is less likely to elicit allergic reactivity in a sensitive patient. To perform the test, 0.1 mL of the vaccine is injected by the intradermal route into shaven skin on the lateral thorax. Similar injections are performed with the diluent (or sterile saline solution) as a negative control and histamine as a positive control. Injection sites are observed and wheal development is measured after 15 to 20 minutes. The presence of a wheal at the vaccine site indicates a positive response to the vaccine, that is, the vaccine contains one or more antigens that are able to stimulate IgE present on tissue mast cells of the patient.

LOCAL VACCINE REACTIONS: ARTHUS REACTION

Although the immediate type I IgE-mediated responses to vaccine-associated nontarget allergens can be serious, a less serious, but annoying response to

vaccination can also occur. The Arthus reaction is mediated by immune complexes, a typical type III hypersensitivity response.[9] Typically the Arthus reaction occurs within 24 hours after the vaccine is given and is localized to the injection site. The area becomes swollen and painful. On histologic examination the tissue shows vasculitis with infiltration of neutrophils. Sometimes local hemorrhage can also be a feature of this response. These responses occur because there is circulating IgG, specific for either target or nontarget antigens. When more antigen is injected into the tissue, immune complexes form within and around dermal blood vessels. Fixation of complement by these complexes causes production of chemotactic factors, C3a and C5a, which cause degranulation of mast cells and neutrophil chemotaxis (**Fig. 2**). The resulting inflammation leads to swelling and pain in the area. Generally after 2 to 3 days the lesion resolves. However, the lesson learned is often that the patient is not likely to need another booster immunization in the near future (if an older patient, possibly not at all). Determination of a titer against the vaccine target antigen is a logical step toward deciding when and if to revaccinate the patient. The Arthus reaction should be differentiated from an adjuvant reaction.

FELINE VACCINE–ASSOCIATED FIBROSARCOMA

Like vaccine-induced anaphylaxis the development of fibrosarcomas in response to vaccination in cats is rare (estimated between 1 in 1000 and 1 in 10,000 vaccinated cats).[10] Nonetheless, if the cat affected is your patient or your pet, that statistic is not particularly comforting. The development of fibrosarcoma at the injection site of a vaccine began being recognized in 1991. Administration of adjuvanted killed vaccines (rabies and feline leukemia) is associated with development of these tumors.[10] Over the years a variety of studies have been performed to determine the cause of the response, and associated host and vaccine factors. In 1996 a Vaccine Associated Feline Sarcoma Task Force was initiated with resultant changes in feline vaccine protocols and procedures. A nonadjuvanted rabies vaccine for cats subsequently became available but according to a recent study in Canada, the incidence of post-vaccine fibrosarcomas has not shown a significant decline.[10]

One result of the recognition of vaccine-associated fibrosarcomas in cats has been an effort to put vaccines in specific sites, such as feline leukemia as far down on the left leg as possible, and rabies as far down on the right leg as possible. This process serves two purposes: to determine which vaccine is causal in the event that a tumor does occur, and to make it possible to save an animal's life by leg amputation should a tumor occur. Administration of vaccines in the intrascapular area makes it nearly impossible to surgically remove tumors in that site.

VACCINE-INDUCED DISEASE EXACERBATION: A BARRIER TO VACCINE DEVELOPMENT

When patients who have been vaccinated against a particular pathogen are exposed to that pathogen, if the vaccine is effective the patient should either not develop the disease or perhaps develop only a mild form of the disease. There are some instances in which a vaccine not only failed to protect but actually caused a more severe disease than would be expected in an unvaccinated patient. The cause of vaccine-induced disease enhancement is induction of an immune response that is pathogenic rather than protective. This type of response has been documented first in human children inoculated with formalin-inactivated alum adjuvanted respiratory syncytial virus vaccine, then in bovine respiratory syncytial virus vaccinated calves.[11] Research has shown that in the latter case the killed vaccine stimulates a strong T-helper type 2 response, with predominant interleukin (IL)-4 production and IgE antibodies directed

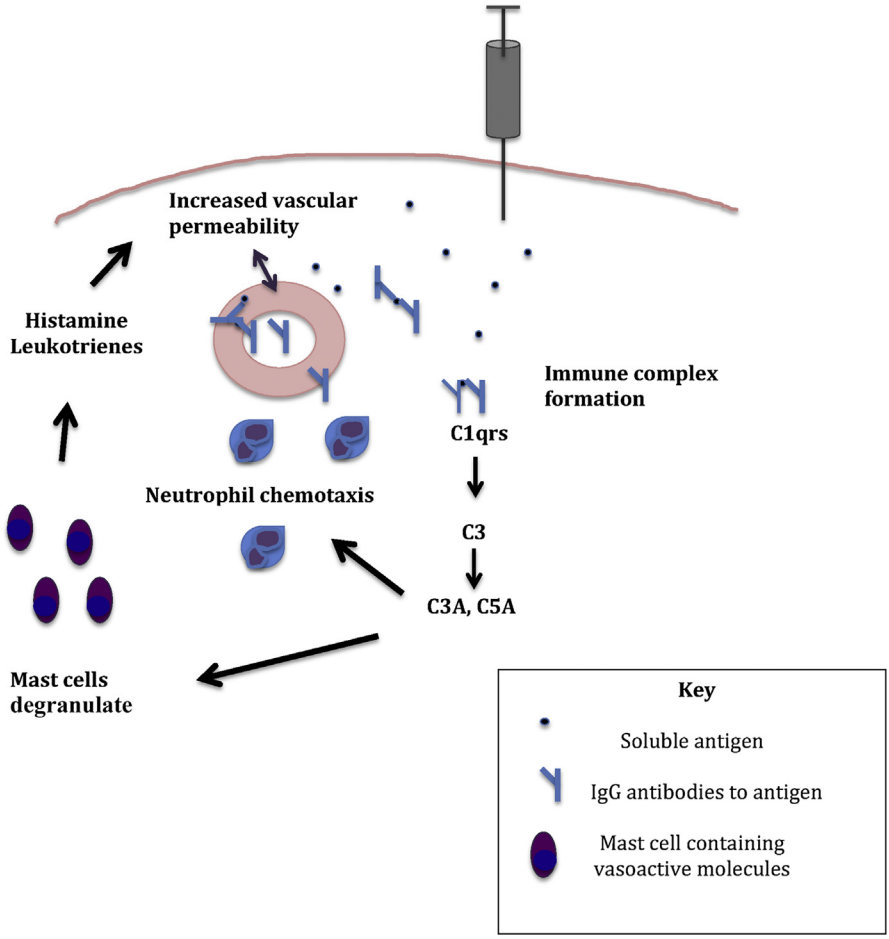

Fig. 2. The clinical syndrome called the Arthus reaction results from a localized type III hypersensitivity reaction. The Arthus reaction is usually seen in animals that have been vaccinated many times (eg, an older dog that has had yearly vaccines for many years). In the patient that has made high levels of IgG antibodies to the vaccine antigens, there is IgG in the interstitial tissue fluids and in the blood. When the vaccine antigens are introduced they bind to the antibodies creating immune complexes, complement is fixed, and C3a and C5a are produced. These small by-products of complement fixation cause mast cells to degranulate and release histamine with consequent increased permeability of the local blood vessels, allowing more IgG to leave the blood vessels and allowing immune complexes to penetrate the vessel walls. Chemotaxis of neutrophils is also stimulated by these chemotactic factors and an accumulation of neutrophils occurs in the area of the injection. The end result is an inflamed, swollen area that appears hours after the injection and can last for several days.

against viral proteins.[12] For viral clearance the more effective immune response is a T-helper type 1 response, with production of interferon gamma. Research performed using cotton rats and mice as models have shown that when the immune system's first encounter with the respiratory syncytial virus/bovine respiratory syncytial virus is with the killed virion, modulation of the immune response favors the T-helper type 2

response; whereas when that first encounter is with live (or a living attenuated) virus a more balanced immune response results. Recent research on respiratory syncytial virus vaccination using a cotton rat model has shown that when the viral antigen is inert (eg, a subunit fusion protein) the dose is an important factor that determines whether vaccine exacerbation occurs.[13] Our group found that to also be true for the formalin inactivated alum adjuvanted bovine respiratory syncytial virus vaccine.[12]

Feline infectious peritonitis (FIP) is another disease that has been associated with vaccine-induced enhancement. FIP is caused by a coronavirus, which is thought to have mutated from the common feline enteric coronavirus. The pathogenesis of FIP is complex, but the most recent data suggest that macrophages play an important role in harboring and propagating the virus.[14] A vaccine for FIP that was previously on the market induced IgG against the virus, which for many infectious agents would be protective. However, for FIP these antibodies opsonized virions for enhanced phagocytosis by macrophages, thus facilitating spread of the virus within the cat. As with dengue, a tropical disease affecting humans, FIP is also associated with antibody-dependent enhancement of disease. In the presence of nonneutralizing IgG human patients infected with dengue virus can progress to hemorrhagic fever or dengue shock syndrome.[15] The currently accepted explanation for this pathogenesis involves opsonization of the virus by the nonneutralizing IgG with subsequent immune complex binding to Fc receptors and enhanced cell infection caused by improved phagocytosis. Cats infected with FIP virus type I and passively immunized with FIP antibody against virus type 2 had a significantly lower survival rate than cats that did not receive the passive antibody.[16] The spike protein (S) is the target for neutralizing antibody production. A recombinant vaccinia virus vectored vaccine containing the gene coding for the S protein was tested in kittens subsequently infected with virulent FIP. Vaccinated kittens died earlier than similarly infected control kittens.[17] In another study DNA vaccination was used to attempt to induce a cell-mediated immune response to FIP virus. Codelivery of plasmids containing IL-12 and the nucleocapsid (N) and membrane protein (M) was used in a prime-boost schedule before virulent FIP challenge. The infected kittens that received the vaccine containing the IL-12 gene had a shorter survival time that those receiving the plasmid coding for the two FIP antigens (N and M) without the IL-12, thus suggesting some degree of enhancement.[18]

VACCINATION AND AUTOIMMUNITY

In recent years there has been much conjecture and some case histories that suggest a possible connection between overstimulation of the immune response with excessive vaccination and the development of autoimmune disease, such as immune-mediated anemia. Evidence for this is scant but there are a few studies that substantiate a connection. A controlled retrospective study on dogs that developed immune-mediated hemolytic anemia (IMHA) compared dogs that developed IMHA within a month after vaccination with dogs that developed IMHA more than a month after vaccination. The study found that a significant number of the 58 study dogs (26%) had developed IMHA within a month of vaccination. The mean number of days postvaccination was 13 days. In contrast the control group of dogs did not show an association between vaccination and development of IMHA. The vaccines used in this study were common: distemper, hepatitis, parvovirus, leptospirosis bacterin, and *Bordetella bronchiseptica* bacterin from a variety of pharmaceutical suppliers. The authors conclude that their study defines a temporal association between vaccination of dogs with commonly used vaccines and development of IMHA.[19] In contrast, there are several other published studies that fail to associate vaccination

with development of IMHA in dogs. These include a study by Carr and colleagues[20] in which a group of 72 dogs with IMHA were compared with 29 dogs in a vaccine control group. No significant differences were found when the temporal relationship between vaccination and initiation of disease was examined.

Autoimmune diseases in dogs are associated with certain genetic haplotypes[21] and thus it is not surprising that one sees more autoimmune disease in certain breeds. For example, the Samoyed has a much higher[21] chance of developing diabetes mellitus than most other breeds. Autoimmune thyroiditis is more common in the Labrador retrievers. Although there are some autoimmune diseases for which there is a direct connection to a particular infection or other instigating factor, in most cases the factors that contribute to the development of an autoimmune response are likely multiple and for the most part unknown.

The notion that vaccination causes autoimmunity is almost certainly false. However, it is likely that a combination of genetics, environmental factors, and overstimulation of the immune system (which can occur as a result of overvaccination) contribute to development of many autoimmune diseases. It is not uncommon to hear a case history of a middle-aged dog who has had yearly vaccines since puppyhood develop acute hemolytic anemia 2 weeks after a visit to her veterinarian for annual booster vaccination. In such a patient stimulation of a "cytokine storm" by multiple vaccine antigens and adjuvants could provide T-cell help to B cells that are self-reactive, but normally kept in check as a result of the absence of T-cell help. The concept of bystander cell activation has been suggested as a potential result of overstimulation of the immune system by injection of multiple vaccines at once as often as every 6 to 12 months. Cytokine production in the localized microenvironment of lymphoid tissues may lead to promiscuous stimulation of potentially autoreactive B cells. Self-tolerance is achieved by the removal of self-reactive T cells in the thymus during fetal development, but tolerance at the level of the B cell is often maintained because of the absence of T-cell help. Acquisition of T-cell help by self-reactive B cells may cause autoantibody production and subsequent autoimmune disease.[22]

In one study the presence of antithyroglobulin antibodies after routine vaccination was examined in pet dogs and research Beagles. Hypothyroidism is one of the more common autoimmune diseases in humans and dogs; it is estimated that about 50% of hypothyroid dogs have autoimmune thyroiditis. In this study 20 research dogs and 16 pet dogs were followed after vaccination with multivalent vaccine with or without rabies vaccine. The research dogs were vaccinated seven times until 52 weeks of age and then every 6 months until 4 years of age (much more frequently than recommended). The pet dogs were all older than 2 years of age and received a booster vaccine and were checked 14 days later. A thyroid profile consisting of T4 and thyroid-stimulating hormone levels and baseline complete blood count and blood chemistry was performed. In addition, antibodies to bovine and canine thyroglobulin were evaluated. Antibovine and anticanine thyroglobulin antibodies were found in sera from vaccinated dogs. In the pet dogs the anticanine thyroglobulin antibodies were significantly increased and those specific to bovine thyroglobulin were not. The dogs that received the multivalent vaccine without the killed alum adjuvanted rabies vaccine did not show a significant increase in antithyroglobulin antibodies when compared with unvaccinated control animals, but dogs that received the rabies vaccine showed a significant difference from those groups that did not receive the rabies vaccine. There is no known correlate with the development of autoimmune thyroiditis and the role of antibody in pathogenesis of canine Hashimoto's thyroiditis is still being debated. However, the

authors suggest that the presence of bovine thyroglobulin in the fetal bovine serum used to assist cell culture propagation may play a role in vaccine-induced stimulation of this immune response.[23] Stimulation of antibodies to canine thyroglobulin by immunization with bovine thyroglobulin (inadvertently as a vaccine nontarget antigen) could solicit T-cell help for self-reactive B cells by exposure to cross-reactive epitopes (Fig. 3).

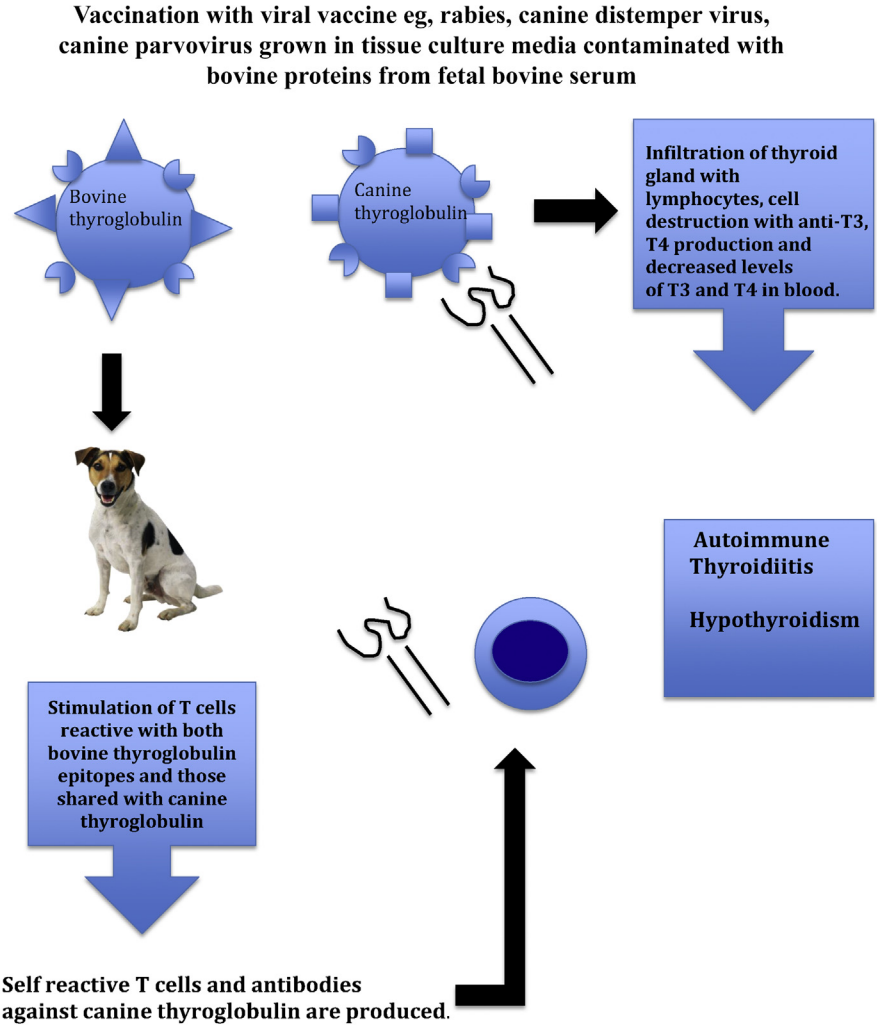

Fig. 3. Autoimmune thyroiditis (Hashimoto's thyroiditis) occurs when activated T lymphocytes attack the thyroid gland and cause cell necrosis. The production of antibodies specific for thyroid antigens is usually another feature of the disease. The resulting destruction of the glandular tissue causes a lack of the thyroid hormones, thyroxin (T3, T4), and with it clinical signs relevant to the hypothyroid state. One hypothesis as to how this occurs is that the presence of bovine thyroglobulin in vaccines (nontarget antigen) stimulates a cross-reactive epitope in the canine thyroid and recruits autoreactive T cells, which then mediate the immune destruction. The disease is more common in certain dog breeds; thus, genetics undoubtedly influences this response.

GENETICS AND AUTOIMMUNITY

The link between autoimmune disease and genetics is well established. For example, it is known that if a person has the major histocompatibility complex B27 allele he or she has a strong likelihood of developing the autoimmune disease ankylosing spondylitis.[22] Canine histocompatibility antigens (DLA) have been linked to a variety of autoimmune diseases. The relative risk of developing many of the currently recognized autoimmune diseases of dogs is higher in dogs with certain DLA haplotypes.[21] The notable increased incidence of particular autoimmune diseases in specific breeds has led to analysis of DLA haplotype associations. The high incidence of diabetes mellitus in Samoyed dogs compared with the rare occurrence of this disease in the Boxer breed led to an evaluation of 460 cases and 1047 controls which revealed a DLA DQ haplotype that was significantly reduced in cases with diabetes mellitus.[24] In another study Cocker Spaniels, a breed with an increased incidence of IMHA, were evaluated for DLA haplotype DLA-DQB1 prevalence of IMHA. Affected and unaffected Cocker Spaniels were evaluated and no significant difference was identified.[25] However, other studies have identified in German Shepherd dogs and Pembroke Welsh Corgis that DLA-DQB1 duplication is a risk allele for exocrine pancreatic insufficiency.[26] Nova Scotia duck tolling retrievers are predisposed to an immune-mediated disease resembling systemic lupus erythematosus in humans. An association with a DLA class II haplotype was found to be highly significant for the development of the lupus-like syndrome in homozygous dogs.[27]

In recent years the veterinary profession has taken a closer look at the duration of immunity for core canine and feline vaccines. Studies have been published that confirm a longer duration of immunity that lasts for at least 3 years for core vaccines. This information has instigated a change in vaccination recommendations: the American Veterinary Medical Association, American Animal Hospital Association, and the Association of Feline Practitioners have all determined that after puppy/kitten vaccines and a 1-year booster, in subsequent years core vaccines need be given only every 3 years. This schedule is expected to reduce the unnecessary immune stimulation and if frequent vaccination is a factor in development of autoimmunity, the incidence of these diseases may be expected to decrease. Increasing research to create better knowledge of the genetic predispositions for autoimmune disease in particular dog breeds coupled with alterations in patterns of vaccination will likely be the key to prevention of an adverse interaction between vaccine practices and canine genetic factors.

SUMMARY

In this article a variety of potential detrimental effects of vaccination are described. It is important for veterinarians to be aware of these for appropriate modification of immunization schemes for individual patients as needed. However, it must be emphasized that the number of pets that suffer from vaccine reactions is extremely low and that most available vaccines are safe and efficacious. Vaccination of animal companions is an important part of an overall health program and should be conducted according to the current standards.

REFERENCES

1. Frick OL, Brooks DL. Immunoglobulin E antibodies to pollens augmented in dogs by virus vaccines. Am J Vet Res 1983;44(3):440–5.

2. HogenEsch H, Dunham AD, Scott-Moncrieff C, et al. Effect of vaccination on serum concentrations of total and antigen specific immunoglobulin E in dogs. Am J Vet Res 2002;63(4):611–6.
3. Tater KC, Jackson HA, Paps J, et al. Effects of routine prophylactic vaccination or administration of aluminum adjuvant alone on allergen-specific serum IgE and IgG responses in allergic dogs. Am J Vet Res 2005;66(9):1572–7.
4. Ohmori K, Masuda K, Maeda S, et al. IgE reactivity to vaccine components in dogs that developed immediate-type allergic reactions after vaccination. Vet Immunol Immunopathol 2005;104(3–4):249–56.
5. Gershwin LJ, Netherwood KA, Norris MS, et al. Equine IgE responses to non-viral vaccine components. Vaccine 2012;30(52):7615–20.
6. Behrens NE, Gershwin LJ. Immune modulation of T regulatory cells and IgE responses in horses vaccinated with West Nile virus vaccine combined with a CpG ODN. Vaccine 2015;33(43):5764–71.
7. de Silva R, Dasanayake WM, Wickramasinhe GD, et al. Sensitization to bovine serum albumin as a possible cause of allergic reactions to vaccines. Vaccine 2017;35(11):1494–500.
8. Chernin LR, Swender D, Hostoffer RW Jr. Cracking the shell on egg-hypersensitive patients and egg-containing vaccines. J Am Osteopath Assoc 2011;111(10 Suppl 6):S5–6.
9. Tizard I. Veterinary Immunology. Chapter 30. 9th edition. Philadelphia: Saunders; 2013.
10. Wilcock B, Wilcock A, Bottoms K. Feline postvaccinal sarcoma: 20 years later. Can Vet J 2012;53(4):430–4.
11. Gershwin LJ, Schelegle ES, Gunther RA, et al. A bovine model of vaccine enhanced respiratory syncytial virus pathophysiology. Vaccine 1998;16(11–12):1225–36.
12. Kalina WV, Woolums AR, Berghaus RD, et al. Formalin-inactivated bovine RSV vaccine enhances a Th2 mediated immune response in infected cattle. Vaccine 2004;22(11–12):1465–74.
13. Schneider-Ohrum K, Cayatte C, Bennett AS, et al. Immunization with low doses of recombinant postfusion or prefusion respiratory syncytial virus F primes for vaccine-enhanced disease in the cotton rat model independently of the presence of a Th1-biasing (GLA-SE) or Th2-biasing (Alum) adjuvant. J Virol 2017;91(8) [pii: e02180-16].
14. Tekes G, Thiel HJ. Feline coronaviruses: pathogenesis of feline infectious peritonitis. Adv Virus Res 2016;96:193–218.
15. Wang TT, Sewatanon J, Memoli MJ, et al. IgG antibodies to dengue enhanced for FcγRIIIA binding determine disease severity. Science 2017;355(6323):395–8.
16. Takano T, Kawakami C, Yamada S, et al. Antibody-dependent enhancement occurs upon re-infection with the identical serotype virus in feline infectious peritonitis virus infection. J Vet Med Sci 2008;70(12):1315–21.
17. Venneme H, de Groot RJ, Harbour DA, et al. Early death after feline infectious peritonitis virus challenge due to recombinant vaccinia virus immunization. J Virol 1990;64:1407–9.
18. Glansbeek HL, Haagmans BL, te Lintelo EG, et al. Adverse effects of feline IL-12 during DNA vaccination against feline infectious peritonitis virus. J Gen Virol 2002;83(Pt 1):1–10.
19. Duval D, Giger U. Vaccine-associated immune-mediated hemolytic anemia in the dog. J Vet Intern Med 1996;10(5):290–5.

20. Carr AP, Panciera DL, Kidd L. Prognostic factors for mortality and thromboembolism in canine immune-mediated hemolytic anemia: a retrospective study of 72 dogs. J Vet Intern Med 2002;16(5):504–9.
21. Tizard IR. Veterinary immunology. Chapter 34. 9th edition. Philadelphia: Saunders; 2013.
22. Murphy K, Weaver C. Janeway's immunobiology. 9th edition. Garland Sciences; 2016.
23. Scott-Moncrieff JC, Azcona-Olivera J, Glickman NW, et al. Evaluation of antithyroglobulin antibodies after routine vaccination in pet and research dogs. J Am Vet Med Assoc 2002;221(4):515–21.
24. Kennedy LJ, Davison LJ, Barnes A, et al. Identification of susceptibility and protective major histocompatibility complex haplotypes in canine diabetes mellitus. Tissue Antigens 2006;68(6):467–76.
25. Threlfall AJ, Boag AM, Soutter F, et al. Analysis of DLA-DQB1 and polymorphisms in CTLA4 in Cocker spaniels affected with immune-mediated haemolytic anaemia. Canine Genet Epidemiol 2015;2:8.
26. Evans JM, Tsai KL, Starr-Moss AN, et al. Association of DLA-DQB1 alleles with exocrine pancreatic insufficiency in Pembroke Welsh Corgis. Anim Genet 2015; 46(4):462–5.
27. Wilbe M, Jokinen P, Hermanrud C, et al. MHC class II polymorphism is associated with a canine SLE-related disease complex. Immunogenetics 2009;61(8):557–64.