Ig A Immunological Disorders in the GSD

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General information

Immunodeficiency disorders are defined by a diminished ability by the body to mount an effective immune response to a perceived threat – eg. infection.

Primary immunodeficiency disease is caused by hereditable defects in the immune system. Secondary immunodeficiency disease is a diminished immune response acquired as a consequence of some other primary disease.

Primary immunodeficiencies involving the cell-mediated, humoral, complement and phagocytic systems have all been described in veterinary literature. Defects involving the humoral immune response are associated with a high susceptibility to bacterial infection. Defects involving the cell-mediated immune response are associated with a high susceptibility to viral, fungal and protozoal infections. Defects in the phagocytic or complement system are associated with disseminated infection.

Clinical Signs – depend on the level at which the immune response is defective and range from chronic respiratory and gastro-intestinal signs and skin infections to life threatening conditions.

Ig A dysfunction –a primary Ig A ***dysfunction*** has been described in the GSD and is probably at the root cause of many GSD specific immunological disorders. Aspergillosis in the GSD has been related directly to the Ig A dysfunction and has an almost 100% death rate.

Other disorders seen in the GSD associated with a compromised immune system (usually involving Ig A) includes the following:-

Aspergillosis and other mycoses
Anal furunculosis – almost exclusive to the GSD.
Exocrine pancreatic insufficiency (EPI),
Inflammatory bowel disease (IBD), s
Small intestinal bacterial overgrowth (SIBO) and its related antibiotic responsive diarrhea (ARD),
Ocular disease including Pannus, Plasmoma
Suppurative otitis externa (ear infections)
Skin -Deep Staph pyoderma/folliculitis,
SLE (Systemic lupus erythematosus and immune mediated skin disease, especially discoid lupus erythematosus (DLE).

Degenerative Myelitis – while not considered to be related to Ig A problems, was initially thought to have an immune-mediated basis. However, there have been few studies of the pathogenesis. The exact precipitating causes of the progressive demyelination and axonal degeneration is still poorly understood. There has been a DNA test developed to identify those that are “carrying” the problem, however, not all affected dogs develop the

condition. Other triggering factors that are yet to be determined are postulated at this stage.

Current Understanding of Ig A problems in the GSD.

Ig A is primarily involved in mucous surfaces and skin/mucous surface junctions. This means the major areas involved are the skin, gut, eye and nose.

Current understanding of the Ig A problem show this as a very complex problem with no simple answer at this stage.

1. Measurements of Ig A levels show a wide variation of serum Ig A levels in normal GSD'S.
2. Reduced Ig A levels shown in tears and feaces of normal GSD but this can vary between studies.
3. Ig A serum levels do not appear to reflect mucosal Ig A secretion in the GSD, despite normal to increased Ig A plasma cell numbers in the lining of the gut.
4. It appears that GSD's may have a "block" in the ***transportation*** of Ig A across the intestinal wall into the gut (and possibly other surfaces). Some of the current research involves 2 molecules that transport the Ig A from outside to inside the gut lumen.
5. It has recently been found that dogs can express at least 4 allotypes of Ig A. Interestingly, all GSD's examined so far express just one of these allotypes (type C). This occurs in the Ig A heavy chain hinge region. This could explain or potentially influence the ability of Ig A molecules to bind antigens. (K Allenspach 2009).

It is clear that the GSD is predisposed to a whole slew of immunological or autoimmune diseases, primarily at this stage resulting from a dysfunctional Ig A transport system.

"In the case of bacterial and fungal infectious diseases, it has been proposed that weak immunological defenses at the mucosal or cutaneous surfaces permits the infection to gain foot hold in the body….. The normal regulation of the immune system must be defective to allow an inappropriate attack on self tissues. Most autoimmunity is now considered to have *an infectious trigger*. Both types of disease may be related to an inability of dogs of this breed to deal effectively with infectious agents.
…. The is no simple immunodeficiency in dogs of this breed, and the overall function of the humeral, cell mediated and phagocytic arms of the immune system are generally considered normal. There may however be a defect in the mucosal Ig A production. Serum, tear and salivary Ig A concentrations are usually normal in GSD's, however there is a failure to adequately translocate Ig A across the intestinal epithelial barrier into the gut lumen.
…Current studies are continuing to address the molecular mechanism that underlies this selective defect in mucosal immunity. The laboratory tools are now available to permit further advances in the identification of the gene mutations that may be responsible for defective immunity in this breed." Michael Day 2003.

Systemic

Aspergillosis – commonly affects the nasal cavity and bone – more often seen in long nosed breeds.
Aspergillosis and other systemic fungal infections are usually as a result of inhalation, more commonly in areas where there is higher humidity. Cases of Aspergillosis have been reported around the world, more so in the warmer and temperature climates.

Aspergillosis(and other mycoses)– the disseminated forms ie. where there is spread through out the body, ***the GSD is uniquely susceptible to the severe disseminated forms***. "The cases seen are often relatively young dogs that develop fungal granulomata throughout the body, particularly involving bone and kidney. …generally considered to cause opportunistic infection in immunocompromised individuals". (M.Day 2003)

Age of onset – any age but normally younger dogs around the 2-6 years bracket.
Symptoms – can vary depending on where the infection sets up. The dog may have vague symptoms of ill health, persistent high temperatures and failure to respond to normal antibiotic therapies.
Treatment – getting an accurate diagnosis is the most critical step. X rays on any bone areas that are suspicious, blood tests, culture of urine. The antifungal drugs can be tried but once a GSD's becomes infected, however, ***the odds of the dog surviving are extremely poor*** due to the underlying immunodeficiency of the Ig A system. If the dog's condition does not improve very quickly, it is the kindest thing to consider the dog's welfare above all other issues and do the right thing by the dog.
Numbers seen – Australia wide – less than 5 cases per year.

Skin

Deep Staph Pyoderma (Furunculosis/folliculitis/cellulitis)

Age of onset - almost exclusive to middle aged GSD's, usually over 5-6 years of age, probably a slightly higher incidence seen in females.

Symptoms - often with a history pattern of intense puritis prior to breaking out. Areas affected rump, back, flanks and thighs in a bilaterally symmetrical pattern. Some individuals have more extensive lesions affecting the chest and neck. The head, ears and front legs are rarely involved. Most cases have a pattern of frequent relapses and the condition is thought to have an immunological basis. Bacterial hypersensitivity, genetic predisposing factors, immune deficiencies and hypothyroidism have all been considered as precipitating or complicating factors.

Treatment - consists of periodic courses of antibiotics, and ongoing use of low doses of cortisone 2-3 x weekly or long courses of cyclosporins. Numbers of these cases are low, but due to the severity of the infections that occasionally build up, these dogs require constant care and ongoing medication. Treated carefully, these dogs can be kept comfortable over 4-6 years, but will not cure, and gradually over time may get more severely affected. Severely affected dogs, if not treated adequately, should be euthanaised.
Numbers affected – less than 1%

Dyscoid Lupus Erythematous – cutaneous – predisposed breeds include the GSD, Collie, Sheltie, Siberian Husky and Malamute. Immune mediated skin disease.
Age of onset - varies but usually the cases seen are over 3-4 years of age.
Symptoms – initially depigmentation of nose and lips, this progresses to ulceration, tissue loss and scaring. Ears, eye rims, feet and genitalia may also be affected. Exposure to ultraviolet radiation will acerbate the condition. In the GSD it is primarily to nasal area that is affected.
Treatment - suitable creams (zinc, sun block) and cortisone orally – this is usually ongoing but low level several times a week, more so in summer. This condition is largely controllable. Excessive exposure to summer sun should be avoided. This is an immune system problem. Numbers seen are very small proportionally.

Nasal Keratitis – is part of DLE - see above.

Eye

Pannus (Chronic Superficial Keratitis) – affects the cornea of the eye resulting in the increasing deposition of black pigment across the cornea.This is considered to be an auto-immune disorder due to the chronic nature of the inflammatory response.
Pannus occurs in the older GSD; probably affecting less than 5% of the population. Pannus also occurs in quite a few other breeds including the Pug, Pekingese, American Cocker Spaniel to mention but a few. Environmental factors such as altitude and solar radiation may modify the occurrence of this disease.
Age of onset – usually older than 6 years of age, most are greater than 8-9 years of age.
Symptoms – usually bilateral, symmetrical inflammation of areas of the cornea resulting in patches of variable pigmentation (from pink to black). This reaction often starts at the lateral or lower-lateral edges of the cornea. The pannus (black pigmentation) gradually covers the majority of the cornea and blindness can occur. This condition involves lymphocytic infiltration with expression of inflammatory cytokines and other molecules
Treatment – ***this condition is controllable but not curable***. Long term use of corticosteroid eye drop and/or cyclosporin eye drops can slow the progression of the disease, however the condition can flare up in the hotter months. Treatment is often used daily until there is good control, then ongoing treatment is usually 2-3 x weekly. If the condition flares up, treatment is again stepped up for short periods.
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Plasmoma – similar condition to pannus, however here it is affecting the conjunctiva and predominantly the 3rd eyelids. Not seen very often, affecting GSD's primarily. Incidence within the breed – very low, less than 1%.
Age of onset – usually older than 6 years of age.
Symptoms – inflammation affecting the conjunctiva and the 3rd eye lid. Usually bilateral, can be unilateral. Results in inflamed thickened areas of conjunctiva and the loss of pigmentation and thickening of the 3rd eyelid. The affected tissue is invaded with lymphocyte and plasma cells.

Treatment – like pannus, this condition in controllable to a large degree, but not curable. Similarly treated to pannus. Long term use of corticosteroid eye drop and/or cyclosporin eye drops can slow the progression of the disease, it can flare up in the hotter months. Treatment is often used daily until there is good control, then ongoing treatment is usually 2-3 x weekly. If the condition flares up, treatment is again stepped up for short periods. The cornea in these cases is unaffected.

This is considered to be an auto-immune disorder due to the chronic nature of the inflammatory response.

Gastric Conditions

GSD's are as a breed prone to a number of chronic gastric conditions. These are a group of conditions/disorders that affect the digestion, absorption of food and/or intestinal stability of the GSD. Many of these conditions probably have an allergic or immunological basis (or trigger). On an overview of these types of conditions as they affect dogs, the GSD is certainly over-represented.

The following conditions have all been proven to have an immune system dysfunction/inflammation process underlying their basis. Equally, treatment of these conditions is generally similar – the aim being to minimize allergic/inflammatory responses of the body and stabilize the gut bacteria and lining so that normal digestion and assimilation of food is possible.
The finer points of exactly ***how these allergic or inflammatory responses are triggered*** is the current goal of researchers. Once we know these triggers, we can be far more specific in tuning diets, food types etc such that the incidences of these conditions should diminish significantly over time.

Idiopathic Inflammatory bowel disease (IBD*) –* this is a name covering several different types of diseases, usually classified according to the type of inflammation present and the area of the intestine where the majority of the inflammation occurs. This collective term covers disorders that are associated with persistent or recurrent gastrointestinal signs and are characterized by histological evidence of intestinal inflammation without a specific cause.
As the Ig A system is intricately involved in dampening the body's reaction to gut antigens, any dysfunction in the system will have an immune response reacting to various gut antigens, be it a bacterial product, a food antigen, or a self antigen (autoimmune). The resulting response induces gastrointestinal irritation and inflammation.
Some breeds are more predisposed to more than one type of inflammatory bowel disease – the GSD and the Boxer are certainly of note - and that these diseases are considered to have an immune mediated component.
These chronic conditions are usually seen (on average) in the slightly older dog (antibiotic responsive diarrhea ARD is more commonly seen in younger dogs). "It has been speculated that ARD occurs first, and that prolonged stimulation by the intestinal flora in genetically predisposed individuals, ultimately causes IBD" (K Allenspach 2009).

Age of onset- generally not much under 12 months, more commonly seen over 15 months.
Symptoms – vomiting (intermittent), diarrhea, weight loss, poor appetite.
Diagnosis – care should be taken to ensure that all possible causes of diarrhea and weight loss are thoroughly explored. Test for EPI and bacterial cultures should also be carried out.
Treatment for these dogs diets aims at stabilizing the gut sufficiently that food can be absorbed, minimizing irritation and stabilizing the gut bacterial populations.

The food given should ideally be concentrated, of an easily assimilated form so as to be highly digestible with low residue. Certainly, consideration for low allergenic diets should be considered – wheat and beef free diets should be of prime consideration for GSD's as there is a reasonably high percentage of allergies to these components. Despite these diets, some dogs may have to remain on a combination of drugs including metronidazole, motility modifiers, gut bacteria stabilizers, pancreatic enzyme replacers in some conditions, and/or low doses of cortisone in very refractory cases.

Small intestinal Bacterial Overgrowth (SIBO) and IBD are often linked, particularly in relation to the GSD. SIBO is thought to occur in the younger animal and if not resolved, turns into IBD over time. [ARD mentioned above is technically the same as SIBO].
Symptoms – diarrhea , weight loss, failure to thrive.
Treatment - These cases generally respond to antibiotics such as Tetracyclines, Metranidazole or Tylosin. These dogs are often placed on 4-6 weeks of drugs while the gut is stabilized.
* It is very important that every effort is made to try and sort out the reasons behind the chronic bacterial overgrowth, so the dietary advice given in the IBD section also applies here as well.

Wheat (Gluten) Allergies – these are very common in many breeds. Tests run have suggested that over 30% of dogs suspected of having food allergies are sensitive to gluten. Many of the features seen in gluten allergies are also seen in other types of inflammatory bowel diseases eg. Lympocytic-plasmacytic enteritis, and it highlights the need with this group of diseases to try elimination diets to ensure that what appears as a chronic disease is not a simple allergy driven condition.
Age of onset - Many dogs that exhibit this condition often show few signs prior to 7-9 months of age (the earliest I have seen this is around 5 months), as it takes time to sensitise an individual by continual low grade insult.
Symptoms usually present as failure to maintain body weight, often despite increasing the food intake; chronically loose to sloppy motions.
Treatment As this is around a similar age to the diagnosis of pancreatic insufficiency in GSD's, my first step is to try these dogs on a wheat or gluten free diets for a minimum of 6 weeks and limit the type of meat proteins fed (usually I limit the meat to either chicken or mutton, and cut out beef entirely). If using a dry food, the safest cereal base to use is rice. The other grains that contain some gluten include barley, rye, buckwheat and oats.

I would estimate around 10-15% of GSD's have a definite wheat/gluten sensitivity and this figure can be higher within certain bloodlines. Add in gut bacterial replacers (Protexin, acidophilis etc) and something fine to line the gut (corn flour, slippery elm powder).

Exocrine Pancreatic Insufficiency (EPI) – tests TLI – fasted TLI <2.5mg/L is diagnostic. Low serum cobalamin is associated with EPI and distal bowel malabsorption (poor absorption of food). Low serum folate is associated with proximal small bowel malabsorption, small bowel intestinal bacterial overgrowth may raise serum folate and lower serum cobalamin. It has been postulated that this is could be an inherited condition in the GSD and may be inherited as an autosomal recessive trait.
Age of onset - from 8 months onwards, most commonly from 2-3 years of age.
Symptoms – chronic diahorrea, often pasty coloured motions, weight loss/failure to hold weight. This is considered an immune mediated condition in the GSD, and as mentioned above, these conditions generally are triggered by an allergic or infectious trigger.
Treatment – low fat diets, supplementation with pancreatic enzymes. Some pancreatic enzyme replacers are far better than others *Creon 1000 is currently the best available. These enzymes are most effectively used by placing them into soaked food about 1 hour before feeding to give the enzymes time to start working.
Place these dogs on low allergy diets in addition to pancreatic enzyme supplementation and bacterial gut replacers, and products to line the gut (see above).

If the dog picks up really well over 4-6 weeks (good weight and firm motions), try gradually removing the pancreatic enzyme supplements, if the weight stays good and the motions stay firm, the majority of the problem could have been a chronic allergic response. If the loose motions return and or the dog starts loosing weight, the dog may have to stay on enzyme supplements for life.

Pancreatic Atrophy – basically the same as EPI, as it progresses to Pancreatic Acinar atrophy (ie. the more chronic form). GSD's represent over ½ the cases seen.
Age of onset – in most breeds, this is seen over 2-3 years of age. In the GSD however these dogs are seen at a young age, even so, signs do not appear prior to 8-12 months of age, so presumably sufficient enzymes are produced prior to this time.
Causes are considered abnormal immune mediated response to a bacterial or inflammatory dietary response.
Treatment These dogs require ongoing pancreatic enzyme supplementation.

The number of GSD's affected by pancreatic insufficiency or atrophy, once the chronic allergy cases are eliminated would be quite small, certainly less than a tenth of the number with gluten allergies.

Ensure that the diagnosis of the chronic bowel condition your GSD is diagnosed as having is correct as chronic wheat (gluten) allergy can present a similar picture of poor absorption of food and/or irritable bowel symptoms. Remove wheat/gluten sources from the diet and see if symptoms abate, try a rice based diet, remove beef proteins as well as this is the most common meat based protein that dogs can be allergic to.

Chronic Colitis (Lymphocytic-Plasmacytic) – inflammatory bowel disease, a subtype of IBD, characterised by infiltration of lymphocytes and/or plasma cells into the walls of the intestines, often involving the full thickness of the mucosa. GSD's and Sharpei's may be predisposed.
Age – most present before 6 years of age. Signs vary considerably between individuals in type severity and frequency, increasing over time.
Symptoms chronic diarrhoea, vomiting common, anorexia followed by bouts of ravenous appetite, chronic weight loss, blood in faeces occasionally seen. Thickened loops of gut, enlarged mysenteric lymph nodes.
Causes – infectious (bacterial guardia, salmonella, campylobacter); dietary (food additives, meat or milk proteins, wheat glutens); genetic factors (breed predilections).
Treat low allergy diets. Cortisone and long term antibiotics may be needed.

Eosinophilic Enteritis – inflammatory disease of the small intestine, an uncommon form or subtype of IBD, which is characterised by the infiltration of eosinophils. This affects parts of the colon where eosinophils have invaded various layers deep. Eosinophils are commonly found where allergic and/or parasitic reactions are going on. The GSD, Rottweiler and Sharpei may be predisposed.
Age – younger animals usually less than 5 years of age, but any age can be affected.
Symptoms – intermittent vomiting, diahorrea, anorexia, weight loss, thickened bowel loops.
Causes – immune related, food allergies, parasites.
Diagnosis – involves trying to determine the cause of the ongoing reaction(s). Through worming and dietary elimination trails may be necessary.
Treament with low allergy diets, limited food sources, high digestibility. Long term dietary control may be required. Use of cortisone may be necessary in the short term.

Anal Furunculosis – chronic disorder – very debilitating.
Symptoms - ulceration, inflammation and sinus tract formation around the anus. Dogs are found licking the area fairly incessantly. Small ulcerations appear which when examined penetrate quite deeply into the tissue behind. Over time these become deeper and more extensive.
This condition is almost exclusive to the GSD (95% of all cases), many affected dogs have concurrent intestinal disease (chronic colitis) or other immune related conditions such as deep staph pyoderma. Chronic diarrhea may contribute by increasing soiling of the anal area.

Causes - The major histocompatibility complex (MHC) has been proven to be involved, showing that there is a definite genetic association in affected GSD's. Combined with a broad based and low set tail, there is a reduced aeration of the anal area. With age, there is an increasing inability to raise the tail (due to fusion of the tail vertebrae).
Treament as this condition is considered to be an immune mediated condition, it responds to a variety of immunosuppressive treatments including cortisone, and cyclosporins. Treatment reduces signs, however the condition has a very high recurrence rate, Surgery has a mixed outcome, although some are cleared. In my experience these complete clearances are few and far between, and are more likely to be successful where tackled early on in the condition.
Good local hygiene with trimming of the hair at the base of the tail and on either side of the rectum (creating a 'breezeway effect') can be very beneficial in assisting in controlling the condition.
Numbers affected – probably maximum of 1%

Conclusion to Chronic Gastric problems
The world of immunology and gastroenterology is one that is rapidly changing.
Our understanding of the finer points of what causes these incredible immunological misfirings or over reactions as well as understanding how gastric allergies and infections trigger these unwanted reactions is just beyond our grasp at this time.
Hopefully, over the next 5-10 years as our understanding of the genetics of the underlying molecular processes involved advances, this will have progressed to the stage that we can start to be able to give much better advice and more specific diets that result in minimal disease and a much healthier future for our beloved breed.

References
Michael J Day "Chronic German Shepherd Dog Illness." 2003.
K Allenspach et al "Evidence for a role of innate immunity in the Pathogenesis of Inflammatory Bowel disease in German Shepherd Dogs". 2009.