Proceedings of the
World Small Animal Veterinary Association
Sydney, Australia – 2007

Hosted by:

Australian Small Animal Veterinary Association (ASAVA)

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Next WSAVA Congress

33rd Annual
World Small Animal Veterinary Association
14th FECAVA
Congress

DUBLIN, IRELAND
20th - 24th August 2008
Auto-inflammatory disorders represent a group of conditions characterised by recurrent bouts of systemic inflammation. These disorders are differentiated from auto-immunity due to an absence of antigen-specific T-cells or significant production of auto-antibodies. Recent advances in molecular genetics have helped to define auto-inflammatory disorders and to elucidate the pathogenesis of these conditions.

Examples of auto-inflammatory disorders in people include hereditary periodic fever syndromes (FMF [OMIM249100], HIDS [OMIM260920], TRAPS [OMIM142680], FCAS [OMIM120100], MWS [OMIM191900], CINCA/NOMID [OMIM607115]), granulomatous inflammation (Crohn’s disease [OMIM266600], Blau syndrome [OMIM186580], early onset sarcoidosis [OMIM609464]), complement disorders (Hereditary angioedema [OMIM106100]), pyogenic disorders (PAPA [OMIM604416], CRMO [OMIM259680]), and vasculitis syndromes (Behcet’s disease [OMIM109650]).

Hereditary periodic fever syndromes in people

Recent identification of the molecular causes for these syndromes has led to improved understanding of their underlying cell biology and enabled targeted therapies for these diseases. These disorders illustrate that rapid progress can occur with development of advanced immunologic and molecular tools.

Familial Mediterranean fever (FMF [OMIM249100])

FMF is caused by mutations in the MEFV gene. The MEFV gene encodes for pyrin protein, and is expressed mainly in neutrophils and monocytes. Pyrin is involved in the interleukin 1 inflammatory pathway, and recent work suggests that defective pyrin may lead to augmented inflammation through increased T-helper 1 activity.

FMF is characterised by recurrent and self-limited attacks of fever with abdominal pain and arthralgia. The duration of attacks is usually 2-3 days. Disease severity varies according to the mutation present, and M694V is associated with a more severe phenotype. Development of amyloidosis leading to renal failure is the most important complication of FMF. Colchicine is used to alleviate the symptoms in FMF and is effective in preventing the development of amyloidosis in FMF patients.

Hyperimmunoglobulin D with periodic fever syndrome (HIDS [OMIM260920])

HIDS is caused by mutations in the mevalonate kinase gene (MVK). Mevalonate kinase is a key enzyme in the cholesterol metabolic pathway, and the activity of the enzyme is reduced to 5-10% of normal in HIDS.
Typical symptoms during febrile attacks include cervical lymphadenopathy, abdominal pain, arthralgia and a maculopapular rash. High levels of serum IgD are present, and are often associated with high levels of IgA. In contrast to other hereditary periodic fever syndromes, HIDS is rarely complicated by amyloidosis. Treatment with colchicine, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are not effective. Simvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme preceding MK in the cholesterol biosynthetic pathway. Simvastatin reduced the number of days of illness in HIDS patients when given continuously.

**TNF receptor-associated periodic syndrome (TRAPS [OMIM142680])**

TRAPS is caused by mutations in the TNF receptor 1 (TNFR1) gene, TNFR1A. TNRF1 is normally shed from receptors on cell surfaces, producing a pool of potentially TNF-neutralising soluble TNRF1 in the plasma. Most inflammatory attacks are a consequence of a defect in the shedding of TNRF1, leading to increased cell surface expression and reduced circulating TNRF1.

The symptoms for TRAPS resemble those of FMF, but are of longer duration. Fever, abdominal pain, synovial inflammation, rash, conjunctivitis and periorbital oedema are typical. Corticosteroids are generally effective in TRAPS, but increasing doses are often required to control the signs. Anti-TNF therapy with the recombinant human TNFR (p75)-Fc fusion protein etanercept (Enbrel) has largely replaced corticosteroid treatment of TRAPS.

**Familial cold auto-inflammatory syndrome (FCAS [OMIM120100]), Muckle-Wells syndrome (MWS [OMIM191900]), and chronic infantile neurologic, cutaneous and articular syndrome/neonatal-onset multi-systemic inflammatory disease (CINCA/NOMID [OMIM607115])**

FCAS, MWS and CINCA/NOMID are caused by mutations in the CIAS1 gene encoding cryopyrin. They were once considered three distinct diseases, but actually represent a continuum of clinical severity, with FCAS being the mildest, MWS being intermediate and CINCA/NOMID having the most severe disease. The majority of mutations cluster within a highly conserved NACHT domain resulting in spontaneous caspase-1 activation and excessive interleukin-1β production.

FCAS typically present for episodes of fever, rash, arthralgia and conjunctivitis following exposure to cold. Neurological findings are seen in MWS and CINCA/NOMID. Sensorineural hearing loss occurs in both MWS and CINCA/NOMID, but neurological signs are more severe in CINCA/NOMID, including chronic sterile meningitis, mental retardation and cerebral atrophy. Interleukin-1β antagonism with anakinra is effective in preventing and controlling these disorders.

**Canine auto-inflammatory (hyper-inflammatory) diseases**

There are no proven auto-inflammatory disorders in the dog, but the following breed-specific examples do fulfil the criteria for auto-inflammatory disease with recurrent fever episodes and lack of documented autoimmunity. Sporadic cases of auto-inflammatory disease occur in the veterinary literature, and
access to advanced immunologic and molecular tools will lead to expansion of this category of disorder in the dog.

Familial Renal Amyloidosis in Shar-Pei dogs
A syndrome of recurrent fever and renal amyloidosis has been reported in the Shar-Pei. Fever may be associated with swelling of one or both tarsal joints. Amyloid deposition occurs in several organs, including the kidney, liver, spleen, gastrointestinal tract, and myocardium. Renal amyloidosis and renal failure lead to early death. Colchicine is recommended in Shar-Pei dogs with recurrent fever to prevent amyloid deposition and progression into renal failure. There is no specific diagnostic test for this disorder prior to amyloid deposition, and a presumptive diagnosis is based solely on clinical signs. While interleukin-6 levels are increased during fever episodes, they are inconsistently elevated in these dogs between episodes and cannot be used to screen for the disorder. Renal biopsy and staining with Congo Red is necessary for definitive diagnosis of renal amyloidosis. Familial Shar-Pei fever is similar to Familial Mediterranean Fever in people, but recent genetic work found no mutations in the canine MEFV gene of affected Shar-Pei dogs.

Hyper-inflammatory syndrome in the Weimaraner
Recurrent fever episodes associated with systemic inflammatory signs have been recognised in the Weimaraner breed for several years. Hyper-inflammatory syndrome was coined for this breed, with manifestations including hypertrophic osteodystrophy, aseptic meningitis, post-vaccinal reactions with high fever and/or nodular skin disease and immunodeficiency syndrome. There is likely to be a common underlying cause for these hyper-inflammatory diseases that is yet to be defined.

Hypertrophic Osteodystrophy (HOD)
A major manifestation of the hyper-inflammatory syndrome is hypertrophic osteodystrophy (HOD), which causes pain and lameness associated with swelling of the growth plates in the long bones. Diagnosis of HOD relies on the typical history, clinical signs, and the presence of characteristic radiographic findings showing changes at the growth plate of long bones. Appropriate clinical signs include swollen, painful metaphyses; fever; lameness and reduced appetite. Many dogs have self-limiting small bowel diarrhoea coincident with the onset of the fever and joint pain. Males and females are equally affected, and the age of onset is typically 8-16 weeks of age.

The cause of HOD remains unknown, with earlier speculations of vitamin C deficiency or over-nutrition discounted in more recent times. Low levels of blood antibody IgA, IgM, or IgA are documented inconsistently in HOD affected dogs. A high heritability for HOD (0.68; 95% confidence interval of 0.65 - 0.71) suggests a significant genetic effect, and a molecular analysis is in progress to further our understanding of this disease. Approximately 70% of the Weimaraners diagnosed with HOD have received a recent multi-valent vaccine within 1-2 weeks of the disease onset. Most of these would have been vaccinated within 2-3 days of disease onset. It is important to note that there have been Weimaraners with HOD not receiving vaccines within the
previous 3 weeks. This indicates that vaccination is one trigger for the HOD disease on a susceptible genetic background.

Treatment of HOD in other breeds has traditionally relied on rest, non-steroidal anti-inflammatory drugs (NSAIDs), and opiate analgesics as necessary. In most cases, the disease is self-limiting, and most dogs recover in several weeks. The disease in the Weimaraner is different. The Weimaraner breed is prone to a severe multi-organ inflammatory form of the disease, and can result in death without appropriate treatment. Practitioners should rapidly rule out infectious causes for the fever and bone pain. NSAIDs and rest are appropriate for self-limiting disease, but corticosteroids should be used with severe, progressive disease when radiographic changes in the growth plates are consistent with HOD. Prompt recognition of the disease and appropriate treatment are the keys to a good outcome.

**Antibody immunodeficiency**

Immunodeficiency in the Weimaraner breed is well known, although the cause is poorly understood. Low immunoglobulin levels are the consistent feature in all of these reports. Chronic, recurrent disease involving a variety of tissues including the gastrointestinal tract, skin, urinary tract and central nervous system is typical. Recurrent bacterial urinary tract infections and inflammatory bowel disease have been common diagnoses in these dogs.

**Steroid-responsive (aseptic) meningitis**

Another disease syndrome seen in the Weimaraner is breed-specific meningitis. These dogs present with fever, spinal hyperaesthesia and central neurological signs. The age of onset is older than for pups with HOD, typically between 16-30 weeks of life. Males are more frequently affected. The diagnosis can only be confirmed by spinal tap and cerebrospinal fluid (CSF) analysis. Many of these dogs have required long term treatment with corticosteroids and azathioprine to control the disease, with frequent recurrence noted with premature discontinuation of treatment.

References available on request