Is Canine Degenerative Cruciate Rupture a Consequence of Rheumatic Disease?

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Rupture of the cranial cruciate ligament (CCL) in the stifle is one of the most important orthopaedic conditions of dogs and leads to a large economic burden. The cause of CCL rupture is not known. This ligament is equivalent to the anterior cruciate ligament (ACL) in the knee of humans. Most CCL ruptures in dogs are degenerative, and are not associated with accidental injury. Current surgical treatments, such as tibial plateau leveling osteotomy (TPLO), do not restore weight-bearing to normal and stifle arthritis typically gets progressively worse after surgery. A likely explanation for these findings is that current surgical procedures only treat dynamic stifle instability during weight-bearing, but do not treat passive instability during periods when the affected limb is not bearing weight, or other relevant pathological change. This presentation will review what is known about the cruciate rupture disease mechanism. Clinical Features: Affected dogs usually have a low-grade lameness initially, that precedes development of stifle instability and more severe lameness. Initial low-grade lameness and bilateral arthritis may persist for many months. At surgery, typical findings include palpable instability, indicating complete tearing of the ligament, and arthritic degeneration of the stifle. These findings suggest that degenerative cruciate rupture is a consequence of a pre-existing arthritic condition, with CCL rupture occurring progressively over time, such that in the early phase of the condition, the stifle is stable.

Joint Pathology: Moderate to severe joint inflammation, or synovitis, is typically seen, usually without full thickness cartilage loss. The synovium or joint lining contains a mixed population of inflammatory cells, which includes T lymphocytes, the inflammatory cell type that has a pivotal role in development of immune-mediated rheumatic arthritis conditions. These findings suggest that degenerative cruciate rupture is an oligoarthritis, which is defined as an inflammatory arthritis affecting ≤ 4 joints. The cell populations present within the stifle synovium suggest that inflammation is driven by a specific immunologic trigger. Relationship of synovitis to stifle instability: The classical paradigm for development of stifle arthritis in dogs with degenerative cruciate rupture suggests that synovitis is largely a consequence of degenerative cruciate rupture and development of stifle instability. This is supported by the fact that surgical cutting of the CCL in experimental dogs leads to synovitis. However, in dogs with mild lameness and a stable stifle, stifle arthritis is also found. These findings suggest that the inflammatory stifle arthritis that precedes development of joint instability is a key factor promoting progressing CCL weakening and eventual mid-substance rupture.

What are the key factors that promote degenerative cruciate rupture? Several factors may contribute to development of degenerative cruciate rupture. These include: (1) stifle anatomy; (2) altered ligament composition and metabolism in predisposed breeds; (3) age-related ligament degeneration; and (4) synovitis. Progressive CCL rupture is associated with up-regulation of ligament matrix turnover, fragmentation of matrix collagen, and loss of fibroblasts from the CCL tissue. Recent studies of the microscopic blood vessel supply to the CCL and the overlying synovial layer lining the stifle joint suggest that the ligament derives most of its nutrition from synovial fluid. Therefore, inflammation of the synovium adjacent to the CCL tissue may have a profound effect on ligament collagen metabolism. These concepts are supported by experimental

studies in which induction of stifle synovitis caused significant degradation in the CCL tensile strength to 29% of control by 6 weeks. In control stifles, the typical mode of cruciate failure during biomechanical testing involved fracture of bony attachment sites; with induction of synovitis, the most common mode failure was mid-substance rupture. These findings suggest that the classical paradigm between synovitis and cruciate rupture needs to be updated and that the dogs with mild lameness, stable stifles and incipient cruciate rupture are typically affected with an oligoarthritis, with joint inflammation often affecting both stifles.

What causes stifle oligoarthritis in affected dogs? The immunologic trigger for canine stifle oligoarthritis is not known. This arthritis condition may be a form of autoimmune disease, in which immune defenses become directed to the patients own tissues. Autoantibodies to collagen may contribute to joint inflammation, but are not a primary causative factor. Translocation of bacterial material to the stifle is a common event and is associated with development of the cruciate arthropathy. Bacterial material is often detected in human joints affected with arthritis, although whether this is a cause or a consequence of the arthritis is controversial. In humans, it is well documented that specific variations in immune defense genes influence the risk of developing chronic arthritis. These data suggest that the presence of bacterial material within the stifle may be a key pro-inflammatory factor triggering chronic synovitis in dogs. Host-bacteria interactions likely involve genetic predisposition.

Future Directions: Improved understanding of the mechanism that leads to degenerative cruciate rupture in the dog will facilitate development of new strategies for diagnosis and treatment of stifle oligoarthritis, including ligament repair. Identification of clinically relevant markers for stifle oligoarthritis will improve diagnosis of the early phase of the, arthropathy. Clinical trials will be required to determine whether antibiotics or disease-modifying anti-inflammatory therapy can reduce joint inflammation and the risk of progressive arthritis and the risk of degenerative cruciate rupture. Identification of at-risk dogs will be facilitated by determining whether specific genotypes confer susceptibility to stifle arthritis in the dog.

Biographical Profile

Dr. Peter Muir obtained his veterinary degree in 1985 from Bristol University. After working in practice, he returned to Bristol obtaining a PhD in veterinary science in 1990. He then moved to the University of Sydney to undertake training in small animal surgery, obtaining a Masters degree in 1992. He completed his surgery training at the University of Wisconsin-Madison and became a Diplomate of the American College of Veterinary Surgeons in 1995. After periods on faculty at the University of California, Davis and the Royal Veterinary College, he returned to Madison as a faculty member, where he is an Associate Professor.

Dr. Muir's research has been supported by the following grants:

2405: Inhibition of Collage no lysis in Canine Cranial Cruciate Ligament During Rupture
741: Polymicrobial Bacteria-Associated Inflammatory Stifle Arthritis/Degenerative Cranial Cruciate Ligament Rupture in Dogs

Is Canine Degenerative Cruciate Rupture a Consequence of Rheumatic Disease? - conference notes

Why is this important?

AVMA Council on Research

-$13 billion in gross sales by Biopharma and Food industries for companion animals and horses in 2005

-vs $16 million on research

America spends

Arthritis

-OA/osteoarthritis and degenerative joint disease

Hard to precisely define

Classically includes cartilage damage

Know seen as inflammatory disease

ACL injuries cause 20% of all lameness in dogs

Clinical features

Often bilateral signs

Prodromal lameness precedes progressive mid-substance rupture

Effusion with a stable stifle or minimal instability

Radiographic signs of arthritis bilaterally

Elevation in markers of joint degradation

Clinical features

Taken together, these data suggest cruciate rupture is a consequence of a pre-existing occurrence of arthritis

Joint Pathology

Moderate to severe inflammation

Typically little cartilage loss

T and B lymphocytes

Activated joint lining cells (macrophages)

Antigen-presenting cells

Up-regulation of pro-inflammatory gene expression

Flow Cytometry

Isolate inflammatory cells from affected stifle joints

Label the cells with a fluorescent antibody for cell surface markers

Count the labeled cells

Cathepsin S is an important therapeutic target for immune inflammatory disease

Tartrate-Resistant Acid Phosphatase regulates maturation of antigen-present cells

T Lymphocytes

Inflammatory pathways involve both innate and adaptive immune responses

Promote development of degradative cytokine network

Joint inflammation can persist throughout the rest of their life

*Taken together, these data suggest the cruciate rupture is an oligoarthritis – arthritis of four or more joints.
Synovitis precedes cruciate rupture and development of stifle instability – arthritis comes before cruciate rupture

Joint inflammation and stifle oligoarthritis precede and contribute to cruciate degradation and rupture

What causes oligoarthritis
- Immunologic trigger is unknown -Autoimmune disease?
- Exposure of collagen neoepitopes and deVelopment of auto-antibodies
- Bacterial infections?
  - DNA has been found through PCR techniques
  - Mixtures often included borrelia
  - 13 of 14 affected dogs had bacterial DNA in the joint
  - Therefore normal stifle is sterile
  - Mixtures of bacterial DNA similar to populations with arthritis

In human arthritis it has been found that bacterial DNA has been found and thus causes inflammation. So a weakened immune system may not be able to deal with these bacteria.

Management goals
- Search for biomarkers for prodomal oligo
  - Lameness with stable stifle
- If stifle is unstable
  - Joint inflammation
  - Stabilize with surgery – ICS, TPLO or LSS

Outcome will be improve with better management.

Afterward, I asked Dr. Muir two questions. In her talk, Dr Root had stated that hormones could possibly be related to cruciate injuries. Had he looked at this or thought about this at all? He responded that there were no credible studies supporting that statement. And he would not consider this further in his study. I then asked him if he had considered skeletal alignment and how that could relate to cruciate injuries. He gave me basically the same answer as with my other question. In my own personal experience, I have a dog that I take to the chiropractor. The chiropractors I have been to, all see a direct correlation in their practices between cruciate tears/ruptures and being out of alignment at the sacral-iliac joint. One of the chiropractors will examine dogs for free who have cruciate injuries to further his study of this. When I spoke to him the last time, 100% of the dogs he treated with cruciate injuries were out of alignment. Things to consider …