Hypertrophic Osteodystrophy (HOD) Update 2007: Irish Setters

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Introduction

Hypertrophic Osteodystrophy (HOD) is a developmental disease in larger breed dogs (commonly, the Great Dane, Alaskan Malamute, Weimaraner and Irish Setter). This disease usually begins between the ages of 3 to 4 months of age. Signs can vary in intensity, and several dogs from one litter may be affected, although at different times. The heritable predisposition of the disease has not yet been documented, and the Irish Setter Health Committee is supporting research into possible DNA HOD markers. The information in this paper is based upon current published literature on HOD, treating 10 cases personally and from telephone consultations/e-mail in 104 cases of Irish Setter HOD over a 5 to 6 year period.

Clinical Signs of HOD

Dogs affected with HOD generally present with lameness or reluctance to walk, and malaise. Early in the disease, the metaphyseal regions of the long bones, i.e. the area between the diaphysis or mid-shaft of long bones, and the physes or growth plates will be tender to digital palpation, slightly swollen and warm when touched by the inside of the examiner's wrist. The disease is usually bilateral, most prominently affecting the distal radial/ulnar metaphysis (above the wrist joints), although the metaphyses of all long bones may be affected less dramatically. More adversely affected individuals are systemically ill, depressed, febrile often reaching 104 – 105.8˚F and anorectic commonly refusing to eat.

Dogs with HOD have episodic symptoms that if not treated will generally experience progressive clinical signs including persistent high fever, anorexia, rapid weight loss and metaphyseal pain that accompanies progressive radiographic signs of epiphysitis and parosteal metaphyseal cuff formation. A few of the chronically affected individuals that survive the acute episode will develop radius curvus, and a smaller number of dogs will die.

Pathophysiological Changes

This is a systemic disease in which the initial lesion occurs in the osteogenic capillary bed of metaphyses responsible for invading and replacing the expanding cartilage model of growth plates involved in endochondral ossification, a developmental mechanism responsible for growth in length of endochondral bones. Lesions of HOD are more prominent in the osteochondral junctions of the most rapidly growing growth plates, e.g. the distal ulna/radius and distal tibia/fibula, although histological lesions are commonly present in metaphyseal physes of less rapidly growing ends of long bones, metacarpal/metatarsal bones, phalanges and growth plates in ribs and vertebral bodies

The initial lesion is necrosis of the capillary loops that invade the cartilage model of the metaphyseal physis. In a normal pup this is a site where the perivascular mesenchyme comes in contact with the bare surface of empty chondrocyte lacunae, differentiates into osteoblasts that apply an initial thin layer of bone tissue to form trabecular systems of primary metaphyseal spongiosa. In the earliest microscopic lesions of HOD where the invading capillary bed and its perivascular envelop of osteogenic precursor cells have died, the germinative layers of the unaffected growth plate continue

to produce cartilage tissue that sends columns of chondrocytes having terminal empty chondrocyte lacuna with mineralized walls into the necrotic tissue at the osteochondral junction. The resulting calcified cartilage lattice void of a bone-covered surface becomes elongated and replaces the primary metaphyseal spongiosa. In the absence of its bony component, the elongated calcified lattice cannot sustain loading from weight bearing and undergoes microfracture and compaction. The band-like zone of the necrotic capillary bed and osteogenic cells undergoes dystrophic calcification. This band also contains a dense neutrophilic exudate that includes macrophages and osteoclasts. The latter two cell types attempt to remove this mineralized debris. Resolution of this initial lesion is recognized radiographically as a zone of increased radiodensity that gradually undergoes a loss of radiodensity following gradual removal of the calcified debris by macrophages and osteoclasts. Onset of healing of the lesion is marked by reestablishment of the osteogenic capillary bed and production of primary spongiosa (Trostel, Pool and McLaughlin).

While the initial necrotic, inflammatory and early healing response is occurring within affected bones at the metaphyseal osteochondral junction, other important but less dramatic changes are taking place in the soft tissues of the metaphysis in the edematous subcutis and fibrous tissue superficial to the periosteum in the so-called parosteal (outside of the periosteum) soft tissues. Immature spindle cells located in the paraskeletal soft tissues are mesenchymal cells left from the period of limb formation that are capable of chondrogenic and osteogenic cell differentiation when properly stimulated. These primitive cells participate along with mesenchymal cells in the osteogenic layer of the periosteum to form the external callus in secondary fracture repair. Apparently, active hyperemia associated with the osteochondral lesions in HOD is responsible for creating edema of the parosteal soft tissues overlying the surface of the metaphyses. Sustained edema and likely inflammatory mediators produced by intra-osseous lesions of HOD stimulate the parosteal mesenchyme to form coalescing islands of cartilage and bone that begin to form an annular extra-periosteal metaphyseal cuff here referred to as a parosteal cuff of mineralized matrix that first becomes apparent in radiographic images from the initial stages of HOD when the transverse HOD line is observed. As this parosteal cuff becomes more radiodense, it progressively obscures the radiographically diagnostic transverse HOD line. With the passage of time, the parosteal bony cuff begins to make initial “spot-well” like attachments through the fibrous periosteum to the cortical bone surface.

In the healing phase of the HOD lesion there is re-establishment of the osteogenic capillary bed at the osteochondral junction, invasion and replacement of the expanding cartilage model of the growth plate by primary spongiosa and resumption of growth in length of the affected bones. Two phenomena occur regarding the parosteal bony cuff at this time. Sequential radiographs demonstrate that the parosteal cuff “appears” to migrate toward the diaphysis; however, in reality, the bony cuff has increased its sites of attachment to the underlying cortical surface, is static and cannot move. But resumption of longitudinal growth by the physis moves the ends of the bone away from parosteal cuff. In the absence of effective treatment, the growth plate disruption may result in reduced bone length or long bone curvature of paired bones, especially at the wrist, e.g., radius curvus. In my experience, this is more common in the Great Dane than the Irish Setter. This less common phenomenon is caused after the parosteal bony cuff has established “spot-welds” connecting the parosteal cuff to the cortical surfaces of the epiphysis and metaphysis and has formed a bridge overlapping the borders of the metaphyseal physis. This bony bridge acts like a staple that sets the physeal border under

sustained compression when physeal growth is re-established and the epiphysis attempts to move away from the parosteal bony cuff.

In fatal cases (Pool, personal communication) in addition to the aforementioned bone lesions finds not only interstitial pneumonia but a diffuse pattern of metastatic calcification of the interstitium and pleural surfaces of the lungs and both epicardial and endocardial surfaces of the heart and rarely a diffuse periosteal new bony response involving the surfaces of both rami of the mandible.

Causes and Predispositions

The cause of HOD remains unknown; however, there are many speculations. In Weimaraners, a hyper immune response to some trigger has been noted (Abels, Harrus, Angles; and Harrus, Waner, Aizenberg). The disease in Weimaraners closely mimics the disease pattern in the Irish Setters. This is the rationale for anti-inflammatory prednisone. Stress may precipitate the disease, including a rapid dietary change over 1 to 4 days. Viral causes and vaccinations have been implicated, although they too just might be one more kind of stress, e.g., 3 to 5 days after the third "combo" vaccine (modified live virus); a second DA_2PPV; or after administration of Rabies vaccines in four- month old puppies (two cases); or after a fourth (often unnecessary) vaccine at 16 to 18 weeks. 70 to 75% of the HOD cases have followed distemper vaccine 3 or 4 days prior. The causal effect of recombinant (rCDV) vaccine (Recombitek®) on the initiation of HOD is not yet known. Vitamin C deficiency also has been speculated as a possible cause; however, there is neither documentation nor a scientific reason for this in the dog, and Vitamin C therapy has not met with scientific success.

An infectious origin has been proposed, and there are reports of hematogenous (blood borne) bacteria producing florid radiographic changes in the metaphyses similar to those of HOD. An experienced radiologist may be necessary to distinguish between possible hematogenous infection, osteomyelitis (bone infection) and HOD radiographic changes. The authors are unaware of any published literature correlating blood culture results with HOD.

Diagnosis

Diagnosis is usually clinical and is supported by radiographic confirmation. Blood panels are always done. In the early stages there is point tenderness in the metaphyses. Radiographic changes including HOD lines and beginning parosteal cuffs may be present as early as one week later. There almost always is an HOD line to aid one in the diagnosis of HOD! Metaphyseal regions may remain mildly affected throughout the course of the disease if well treated, or if poorly treated, may show early irregular widening with abnormal endochondral ossification and growth plate alterations. Severe alterations to the growth plate (most often occurring in the distal ulna), may produce lateral bowing deformities of the front legs (radius-curvus). CBC will show neutrophilia, with bands of 3% or less. One should pay attention to the finding of increased numbers band neutrophils, since that is an indicator of acute sepsis and not a feature of HOD. The normal acceptable range of neutrophil bands is up to 3% or 300 bands, whichever is lower. Values higher than this indicate possible sepsis. One treated HOD case was coughing and had slight pulmonary changes on the radiographs. Pasturella sp. bacteria grew from a trans-tracheal aspirate. This dog was treated for 8 days with antibiotics and NSAIDs; then, the dog was changed to the HOD protocol (with excellent results). We definitely use antibiotics for the first four weeks.

Treatment

In all cases of HOD, treatment is begun by immunosuppresive doses of Prednisone, covered by antibiotics. The dosing regimen is as follows: (1) place the dog

initially on a 1.5 mg/kg/day dose of Prednisone for 4 to 5 days if symptoms show regression, and up to but not more than 7 days if signs are persisting, with half given in the a.m. and the other half in the p.m.; (2) gradually wean down for 6 weeks, cutting the total daily dose by approximately one-half each week; and (3) administer 5 mg of Prednisone every other day for an additional 1 to 2 weeks. Supportive care should be provided as needed. We add oral antibiotics: usually Clavamox, Simplicef or Keflex for 4 weeks. Also, administer antacids (Pepcid b.i.d.) to counter acid secretions stimulated by the Prednisone. With Prednisone treatment, pain medications can be stopped sooner, thereby avoiding possible appetite suppression often associated with pain medications. HOD dogs should not be exposed to possible contagious disease, and owners should be advised not to take their dogs to dog shows, dogs parks, etc. Revaccination for distemper and Parvovirus is usually not necessary as the immune system hyperreacts to these. If in doubt, do distemper and parvo titres indicating possible protective levels. Don't invite relapse with a vaccine before 11 -12 months of age.

The prognosis for most cases is good if this protocol is instituted early. Even in severe cases this protocol has been effective. In our experience, mild cases are not difficult to treat, whereas the more severely affected animals require more aggressive care. Those animals that are not treated early may require IV fluids and electrolytes, nutritional support, and tremendous nursing care to arrive at a successful result. Nursing care is paramount in the successful management of the more severe cases. Mild cases which have been treated solely with non-steroidal anti-inflammatory may respond incompletely, and usually have a subsequent relapse. One pup experiencing a severe relapse had multiple small subcutaneous abcesses. This dog was only on Amoxicillin for a short period of time – possibly a wider spectrum antibiotic (Simplicef) could be used for a longer period of time in such relapse cases.

In two cases of Great Dane HOD, mild puppy strangles (juvenile cellulitis/Staphylococcus plus toxins) were apparent. The use of Prednisone concomitant with antibiotics in cases of puppy strangles was critically important.

Conclusion

Early recognition and appropriate treatment of HOD will hopefully prevent your dog from reaching a critical state. We hope that some of this information will assist in making the early diagnosis of HOD, and welcome your feed back.

Thanks to everyone who has shared information with us about Hypertrophic Osteodystrophy (HOD) cases. This is very informative and important information.

As a result, a few comments are in order:

1. Be sure sepsis or other infection has been ruled out before initiating glucocorticoid therapy (Prednisone, Prednisolone). Do a complete workup, including a full blood panel and chest radiographs. In the initial stage of the disease there should be a radiographic HOD line parallel to the osteochondral junction of the metaphysis often affecting the distal ends of paired long bones for a diagnosis of HOD! However, remember that the parosteal cuff in time will progressively obscure the intial radiographic finding should you be presented with the dog in the later stage of HOD.
2. The dosing regimen is as follows: (1) place the dog initially on a 1.5 mg/kg/day dose of Prednisone for 4 to 5 days if symptoms show regression, and up to but not

more than 7 days if signs are persisting, with half given in the a.m. and the other half in the p.m., (2) gradually wean down for 6 weeks, cutting the total daily dose by approximately one-half each week, and (3) administer 5 mg of Prednisone every other day for an additional 1 to 2 weeks.

3. Cover with Clavamox, Simplicef or Keflex for at least four weeks.
4. Administer antacids (Pepcid twice daily) to counter acid secretions stimulated by the Prednisone.
5. Two HOD cases also evidenced sore mandibles before breaking with overt HOD. These cases showed more tenderness than that normally associated with normal puppy teeth eruptions.
6. Relapses occur in 20 to 25% of cases, and are treated as the initial protocol suggests (with the use of antibiotics again too). One third of these cases can not come off low doses of Prednisone for about 9 – 10 months.

Keep up the good work and the flow of information!
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Trostel, C.T.; Pool, R.R.; McLaughlin, R.M.: Canine Lameness Caused by Developmental orthopedic Diseases, in *Compendium* volume 25(4). Pp282-293; April 2003.

Abeles, V.; Harrus, S.; Angles, J.M., et al: Hypertrophic Osteodystrophy in six Weimaraner puppies with Systemic Signs, in *Vet Rec* 145:130-134; 1999.

Harrus, S.; Waner, T.: Aizenberg, I.; et al: Development of Hypertrophic Osteodystrophy and Antibody Response in a Litter of Vaccinated Weimaraner puppies. *Journal of Small Animal Practice* 43: 27-31, 2002

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