

Hypertrophic osteoarthropathy in wildlife and a review of suggested pathogeneses

Hypertrofisk osteoartropati hos vilt och en översikt av föreslagna patogeneser

Elina Thorsson

Handledare: *Stina Ekman, institutionen för biomedicin och veterinär folkhälsovetenskap, SLU*

Biträdande handledare: *Erik Ågren, avdelningen för patologi och viltsjukdomar, SVA*

Examinator: *Eva Tydén, institutionen för biomedicin och veterinär folkhälsovetenskap. SLU*

Kandidatarbete i veterinärmedicin

Omfattning: 15 hp

Nivå och fördjupning: grund nivå, G2E

Kurskod: EX0700

Utgivningsort: Uppsala

Utgivningsår: 2015

Veterinärprogrammet, examensarbete för kandidatexamen / Sveriges lantbruksuniversitet,
Institutionen för biomedicin och veterinär folkhälsovetenskap

Delnummer i serie: 2015:54

Elektronisk publicering: <http://stud.epsilon.slu.se>

Key words: *Hypertrophic osteoarthropathy, digital clubbing, osteopathy, pathogenesis, etiology, wild, exotic, zoo*

Nyckelord: Hypertrofisk osteoartropati, osteopati, patogenes, etiologi, vilda, exotiska, zoo

Sveriges lantbruksuniversitet
Swedish University of Agricultural Sciences

Fakulteten för veterinärmedicin och husdjursvetenskap
Institutionen för *biomedicin och veterinär folkhälsovetenskap*

TABLE OF CONTENTS

Summary	1
Sammanfattning	2
Introduction	3
Materials and methods.....	3
Literature review	4
Hypertrophic osteopathy	4
The pathogenesis of secondary hypertrophic osteoarthropathy	5
Historical view	5
Main hypotheses.....	5
Review of secondary hypertrophic osteoarthropathy in wild animals	7
Case reports, a summary	7
Discussion	12
References	14

SUMMARY

In this essay suggested pathogenesis of secondary hypertrophic osteoarthropathy (HOA) is reviewed. HOA, characterized by; periostitis, periosteal proliferation of tubular bones and arthritis can develop due to many different underlying diseases. The syndrome is most commonly seen with intra-thoracic malignancy or chronic pulmonary infections. HOA has previously mainly been described in humans and various domesticated species. More recently, through wildlife disease monitoring, cases have also been found among wild animals. This essay also aims to summarize the spectra of wild species in which the syndrome has been reported. Finding a coherent pathogenesis has proven to be difficult. Many theories overlap and are not yet fully investigated. Factors of importance include hypoxia, VEGF, PDGF and prostaglandins, but HOA is often suggested to be idiopathic. It is now obvious that secondary HOA affects a wide range of species. Even though the manifestation of the syndrome differs slightly between humans and animals it is similar in many aspects. Considering the similarities it can be presumed that the same pathogenesis applies for humans, domestic animals and wild animals.

SAMMANFATTNING

I denna uppsats beskrivs olika teorier avseende patogenesen till sekundär hypertrofisk osteoartropati (HOA). Den patologiska bilden av HOA innefattar periostit med typisk periostal proliferation av rörben samt artrit. Syndromet anses kunna orsakas av flera olika sjukdomar som underliggande orsak, men ses oftast i samband med intratorakal malignitet eller kronisk lunginflammation. Äldre litteratur har visat att sekundär HOA drabbar människa och ett flertal domesticerade djurarter. På senare tid har fall också rapporterats hos flera olika vilda djurarter. Denna uppsats syftar även till att sammanställa det spektrum av vilda djurarter där sekundär HOA finns rapporterat. Att finna en sammanhängande patogenes har visat sig vara svårt då teorierna är många, men sparsamt utredda. Faktorer som anses kunna vara inblandade i processen är hypoxi, tillväxtfaktorer som VEGF, PDGF samt prostaglandiner. Men ofta anges orsaken vara idiopatisk. Litteraturgenomgången har klart visat att sekundär HOA drabbar ett stort antal djurarter. Hur syndromet yttrar sig kliniskt skiljer sig något i beskrivningarna mellan människor och djur, men likheterna överväger vilket gör att man kan anta att samma patogenes föreligger hos människa och olika djurarter, inklusive vilda djur.

INTRODUCTION

Hippocrates (Greece, 460 BC) was first to document findings of digital clubbing, i.e. periosteal exostoses. This is believed to be the oldest description of clinical signs in human medicine. Hippocrates described deformed phalanges in association with empyema and strained respiration (Davidson, 1984). Archeological findings of digital clubbing in skeleton of humans (7000 years old) gives emphasis to the early presence of the syndrome (Masson *et al.*, 2013). In more present history, HOA was first described by Bamberger (1889) and Marie (1890). Digital clubbing (periosteal proliferation of tubular bones) is one part of the triad constituting HOA, which also includes periostitis and arthritis (Elewaut, 2005). There have been different perceptions whether all three signs need to be present for accurate diagnosis in humans. These lesions are often seen together with thickening of the skin of the extremities, edema, pain at palpation and stiffness (Ginsburg, 1963). Today the general opinion is that HOA is a progressive syndrome where the symptoms differ over time (Martinez-Lavin *et al.*, 2007). HOA in humans is classified as primary or secondary (see below for definitions).

Despite the severity and the early historical introduction the pathogenesis of HOA is yet to be determined. The wide spectra of underlying causes and the rareness of HOA complicate the research into the pathogenesis of the syndrome. In addition to humans HOA has most frequently been observed in dogs (Brodey, 1971; Salyusarenko *et al.*, 2013), cats (Huang *et al.*, 2010), horses (Jp *et al.*, 1992) and cattle (Guyot *et al.*, 2011). The syndrome is however not limited to domesticated species; as this essay will demonstrate.

The aim of this literature review was to describe the current described hypotheses of the pathogenesis of secondary HOA. The review also aimed to demonstrate the spectrum of wild animal species in which occurrence of secondary HOA have been reported. In this essay wild animals are broadly defined as, and include; undomesticated species, zoo animals and exotic pets.

MATERIALS AND METHODS

This essay is a literature review divided into two parts, the suggested pathogenesis of secondary HOA and a summary of case reports describing the syndrome in wild animals. A web-search was performed in several data-bases; Primo, Scopus, PubMed and Web of Science, using following key words:

- hypertrophic osteoarthropathy, digital clubbing, acropathy, Marie's disease, osteopathy
- causes, pathogenesis, pathogenetic, source, causation, genesis, pathophysiology, aetiology
- wild, undomesticated, exotic, zoo

Regarding the pathogenesis, the search was limited to the years 2005-2015 whereas the case reports were collected without year limitations. In addition to mentioned data-bases I used Google, Google scholar and websites of veterinary pathology and wildlife medicine.

LITERATURE REVIEW

Hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy (HOA) is a progressive syndrome characterized by the presence of bilateral digital clubbing (periosteal proliferation), periostitis and clinical signs of pain and swollen joints defined as arthritis (Sarkar *et al.*, 2012; Klippel *et al.*, 2008). The surface of the affected bones is irregular due to spiculated exostoses. The syndrome is diagnosed by imaging (radiography) and clinical examination (M Martínez-Lavín, 1993).

In animals, the new bone formation usually is concentrated to the diaphyseal region of long bones. Radius, ulna, tibia and the metatarsal bones are in dogs the first regions to undergo formation changes. Pelvis, vertebrae, ribs, and bones of the skull may be involved. In 40 % of human cases, the patients develop articular lesions whereas only 5 % of the dogs show articular lesions (Brodey, 1971). In humans the proximal phalanges, metatarsal and metacarpal bones and distal ends of long bones are the most frequent locations with periosteal proliferation (digital clubbing), consensus reported from WSCO (See The joint pathology center, 2003).

Primary hypertrophic osteoarthropathy, also known as pachydermoperiostosis, is a rare hereditary form of HOA in humans (Sarkar *et al.*, 2012). In addition to periosteal bone proliferation, periostitis and arthritis thickening of facial skin is seen. The facial skin changes are the easiest way to separate primary HOA from secondary HOA (Sarkar *et al.*, 2012). Recently a mutation of the human main enzyme in prostaglandin degradation has shown to be the cause of primary HOA (Uppal *et al.*, 2008).

Secondary hypertrophic osteoarthropathy, formerly named pulmonary hypertrophic osteoarthropathy, is most commonly associated with intra-thoracic malignancies or chronic pulmonary infections (Yao *et al.*, 2009). The changes in the bone tissue is progressive and develop over months to years and are often detected prior to the suggested underlying disease (Salyusarenko *et al.*, 2013). The late diagnosis of the underlying cause contributes to a poor prognosis for individuals diagnosed with secondary HOA.

As an awareness of the syndrome has increased, reports of other primary causes, not concentrated to the thorax, have been suggested. It is now well established that congenital heart disease (Ferreira & Camões, 2013), hepatopulmonary syndrome with liver disease, impaired arterial oxygenation and intrapulmonary shunting (Kaleo Ede, 2008) and chronic inflammatory bowel disease such as ulcerative colitis and Crohn's disease (Oppenheimer & Jones, 1982) also are associated with secondary HOA. Treatment of the underlying disease results in decreased pain, decreased swelling of the limbs and often a remission of the new-formed periosteal bone (Ginsburg, 1963).

The pathogenesis of secondary hypertrophic osteoarthropathy

The pathogenesis of secondary HOA has remained elusive for centuries. Many of the hypotheses concerning the pathogenesis were made in the 19th and 20th centuries and are in some cases based on anecdotes.

Neural influence, circulatory changes and growth factors have been discussed as factors of interest. The theories often overlap which suggests that the pathogenesis of HOA is complex.

Historical view

HOA was in the late 19th century believed to be caused by a toxin derived from the bronchial tract (Marie, 1890; Bamberger, 1891). However, since the symptoms weren't reproducible with sputum, the theory was abandoned (Bamberger, 1891). In the mid-20th century there were few and unproven theories. The conception was, and in some cases still is, that the affected extra skeletal organs send an impulse through the vagal nerve inducing periosteal proliferation with new bone formation (clubbing). The blood flow in the periosteal areas of the limbs was thought to increase due to an unknown mechanism. A small study of only five cases showed decreased swelling of the limbs and pain relief following vagotomy (Flayell, 1956). Hyperemia of the periosteal connective tissue with excess of blood and its nutrients is believed to trigger inflammation (CLUBBING AND HYPERTROPHIC OSTEOARTHROPATHY. : Medicine). However, increased blood flow has been described in several conditions with absence of periostitis and periosteal bone proliferation, which clearly questions that hyperemia is the main cause of clubbing (Ginsburg, 1963).

Main hypotheses

In their review, Yao *et al.* (2009) suggested that the most likely hypothesis of secondary HOA was presented by Dickinson and Martin (1987). The authors suggest that megakaryocytes and clusters of platelets in the distal vasculature of the limbs induce release of platelet derived growth factor (PDGF). Megakaryocytes form in the bone marrow and are released to the circulation. Normally, clusters of megakaryocytes and platelets become trapped or fragmented as they pass through the highly dichotomized pulmonary vasculature (Dickinson & Martin, 1987). Thoracic lesions may cause a pulmonary shunt where this sequence of events would be lost and the clusters of megakaryocytes and platelets reach the systemic circulation and subsequently the peripheral vasculature of the distal limbs where they could activate endothelial cells and release growth factors (Dickinson & Martin, 1987).

In a retrospective study comprising 30 dogs diagnosed with secondary HOA by Salyusarenko *et al.* (2013), a significantly higher platelet count and thrombocytosis was found in the dogs with secondary HOA compared to healthy controls. The dogs with secondary HOA were also found to have significantly higher proportions of shistocytosis (fragmented red blood cells), anisocytosis (different sized red blood cells) and pyrexia (Salyusarenko *et al.*, 2013). The elevated platelet count, thrombocytosis and shistocytosis can be explained by a suspected pulmonary shunt. The pyrexia refers to an ongoing inflammatory process of the bony lesions.

There are contradictory studies on whether hypoxia causes secondary HOA with clubbing or not. Paton *et al.* (1991) report a tenfold presence of clubbing in pediatric patients with hypoxia due to cystic fibrosis, compared to the control group without hypoxia (Paton *et al.*, 1991). A connection between elevated VEGF (vascular endothelial growth factor) and PDGF concentrations and hypoxia has been established in human patients with HOA (Silveira *et al.*, 2000; Atkinson & Fox, 2004). In contrast, a study examining humans diagnosed with secondary HOA associated with liver disease, showed no difference in oxygen tension between the patients and the control group was found (O Epstein, 1979). Also, individuals with an inflamed bowel show increased expression of VEGF-A without evidence of hypoxia (Scaldfarri *et al.*, 2009).

The above described hypotheses involving megakaryocytes and hypoxia are supported by presence of an impaired lung function. PDGF and VEGF are formed when platelets aggregate and the growth factors are regulated by hypoxia (Silveira *et al.*, 2000; Atkinson & Fox, 2004). PDGF is likely to cause changes such as increased blood flow, edema, collagen deposition and endothelial hyperplasia, which proceed clubbing (Atkinson & Fox, 2004). However, an experimental study in rats with intermittent intravenous infusion of PDGF (BB chains) did not result in development of clubbing. The infusion resulted in an increased bone mass and bone strength of the skeleton in the rodents (Mitlak *et al.*, 1996).

VEGF is a growth factor produced by malignant tumors to ensure their vascular formation and nutritional supply. The factor induces edema, vascular hyperplasia, fibroblast proliferation and new periosteal bone formation, all seen in HOA (Ferrara, 2004). Even though PDGF may be considered to be the main growth factor involved in the pathogenesis of HOA (Dickinson & Martin, 1987), it has been noted that elevated levels of VEGF also may induce pathological changes such as edema, vascular hyperplasia, fibroblast proliferation and new periosteal bone formation (Atkinson & Fox, 2004). Elevated levels of VEGF have been seen in patients with both primary and secondary HOA (Silveira *et al.*, 2000).

The most recent hypothesis regarding the pathogenesis of HOA suggests a chronic activation of macrophages (Toovey & Eisenhauer, 2010). The macrophage activation can be triggered by a persistent irritant or hypoxia and lead to elevated levels of growth factors and formation of granulomas (Toovey & Eisenhauer, 2010).

Other circulatory factors such as prostaglandins and hepatocyte growth factor have also been suggested to be involved in the pathogenesis of digital clubbing (Silveira *et al.*, 2000). *In vitro* studies, using rat cell cultures, show that prostaglandins may upregulate expression of VEGF (PGF₂) (Harada *et al.*, 1994) and enhance growth of megakaryocytes (PGF₁) (Cooper & Hou, 1988).

Länge (1994) used an isoquinoline derivate in an experimental treatment of bronchial asthma in rats, and unintentionally induced symptoms corresponding with HOA.

Review of secondary hypertrophic osteoarthropathy in wild animals

Case reports, a summary

The database search for secondary HOA in wild animals resulted in a number of case reports, mainly single affected animals of various species from different genera or families. The database search for HOA in wild animals resulted in a number of case reports, mainly single affected animals of various species from different genera or families. All animals presented in the table below are diagnosed with secondary HOA. The definition of HOA in humans is the triad of lesions, bilateral digital clubbing, periostitis and arthritis (Elewaut, 2005). However, the most common lesions in animals are the periosteal bone proliferations, hence the case report authors have diagnosed HOA when such typical lesions were found.

Table 1, Case reports of secondary HOA in wild animals including suggested and/or potential underlying diseases. The location of the periosteal bone lesions are not always described. ALP= alkaline phosphatase

Animal species	Periosteal bone lesions	Potential underlying disease
Camelidae		
Alpaca, female USA, imported from Chile (Curtis <i>et al.</i> , 1997)	Diaphysis of the metacarpal bones and the proximal phalanges of the right forelimb	Focal chronic pneumonia Chronic interstitial myocarditis
Canidae		
Wolf, <i>Canis lupus</i> Wild, Sweden (SVA, 1997)	Tarsal and metatarsal bones, tibiae, fibulae, femur and the pelvis	-
Fox, <i>Vulpes vulpes</i> female Wild, Sweden (Rubarth SVA, 1933)	Metacarpal bones including the joints, metatarsal bones including the joints, tibiae and the patellae (See front page photo)	Abscending chronic pneumonia and fibrous pleuritis, diplococcus
Fox, <i>Vulpes vulpes</i> male Wild, Sweden (SVA, 1982)	Forelimbs	Pneumonia including pleuritis, isolated bacteria; <i>Clostridium sordellii</i>

Cervidae

<p>Rocky mountain elk, <i>Cervus elaphus nelson</i> two individuals 11- month old</p> <p>Farmed, USA</p> <p>(Joint pathology center, 2006)</p>	<p>Carpal, metacarpal, tarsal, metatarsal bones, radii, ulna and tibiae</p> <p>(In one individual: Asymmetrical bone lysis filled with caseous exudate)</p>	<p>Numerous pulmonary granulomas with coalescing myriad hyphae</p>
<p>Elk, <i>Cervus elaphus</i>, two individuals family group 1 male, yearling</p> <p>Farmed, USA</p> <p>(Ferguson <i>et al.</i>, 2008)</p>	<p>Metatarsal and metacarpal bones, radius, ulnae and calcaneum</p> <p>(Loss of cortical bone in left metatarsus, left tarsal bone and third phalanx of left hind)</p>	<p>Disseminated granulomatous inflammation with intralesional fungal organisms, <i>Aspergillus fumigatus</i>, nodules throughout the lungs, left ventricular myocardium and renal parenchyma</p>
<p>Blesbok, <i>Damaliscus dorcas phillipsi</i> female, 4,5 years old</p> <p>USA</p> <p>(Kenny <i>et al.</i>, 1997)</p>	<p>Right metacarpus with periarticular osteophytes surrounding the fetlock joint, osteoarthritis</p> <p>Midshaft of the left metacarpus</p>	<p>17kg abdominal mass, leiomyosarcoma</p>
<p>White tailed deer, <i>Odocoileus virginianus</i> male, 2,5 years old</p> <p>Free-ranging, USA</p> <p>(Madson <i>et al.</i>, 2009)</p>	<p>Metatarsal diaphyses</p>	<p>25x13x15 intrathoracic mass, eosinophilic granuloma due to fungal infection with <i>Conidiousbolus</i> incongruous</p>
<p>Roe deer, <i>Capreolus capreolus</i> male, adult</p> <p>Wild, Sweden</p> <p>(SVA, 1997)</p>	<p>All limbs extending from the phalanges to the scapulae and femur, respectively</p>	<p>Chronic interstitial pneumonia</p>
<p>Roe deer, <i>Capreolus capreolus</i> male, 3 years old</p> <p>Wild, Germany</p> <p>(Schulze <i>et al.</i>, 2005)</p>	<p>Metacarpal, metatarsal bones and phalanges</p>	<p>Lung abscess and pleuritis</p>
<p>Caspian red deer, <i>Cervus elapus maral</i> male</p> <p>Germany</p> <p>(Ball, 1929)</p>	<p>Extremities</p>	<p>Metastatic pneumonia, <i>necrobacillus</i></p>

Felidae		
Lion, Abyssinian female, 10 years old (Ball & Lombard, 1926)	Femur, tibiae, radius and ulnae (Chronic arthritis of adjacent joints)	Chronic tuberculosis
Siberian tiger, <i>Panthera tigrus</i> 7 years old	Left carpal and metacarpal bones, tarsal joints, tibiae and ulna	Cavernous lung tuberculosis, <i>Mycobacterium bovis</i>
Zoo animal, The Netherlands (Van De Watering <i>et al.</i> , 1972)	Right fifth metacarpal, first phalanx of the fifth toe and associated sesamoid bone Left and right zygomatic process of the skull	
Lion, <i>Panthera leo</i>, female, 25 years old Zoo animal, USA (Bush <i>et al.</i> , 1974)	Long bones including humerus, carpus, tarsus, metacarpal and metatarsal bones Bones of the skull, mandible and pelvis	Chronic pulmonary disease Pulmonary adenoma, 8cm in diameter

Leproidae		
Rabbit, White New Zealand female, 7,5 years old (DeSanto, 1997)	Right tibiae and tarsometatarsal areas Left hind limb appeared slightly swollen, no radiographs taken	Metastatic urine adenocarcinoma, multiple large masses throughout all lung lobes Myocardial fibrosis

Macropodidae		
Red kangaroo (Ladds, Philip W.)	Present, but affected bones weren't presented	Bacterial infection. 25ml pus was extracted from the thoracic cavity
Wallaro, <i>Macropus robustus</i> adult Captivated, Australia (Wayne & Nicholson, 1999)	Radius and ulna, metacarpal bones and phalanges Tibia and metatarsal bones	Intrathoracic lesions: Caseous foci throughout the lungs along with caudal abscess, consolidation, hemorrhage emphysema and pleural adhesions <i>Morganella morganii</i> , <i>Streptococcus</i> and <i>Bacterioides</i> spp. were isolated from the lung tissue

Mustelidae

Mink, Male, 1 year old Long bones and phalanges Bronchogenic carcinoma

Pet animal, Canada

(Wilton & Graesser, 1967)

Palangeridae

Brushtail possum, *Trichosurus* All limbs Nodular mass of distal esophagus extending from the heart to the diaphragm

(Ladds, 2009)

Primates; hylobatidae, hominidae

Gibbon, *Hylobates lar* male, 8 years old Humeri, femora and ulnae Adenocarcinoma of the pancreas

Zoo animal, U.K. Right radii and the proximal and intermediate phalanges of the second right digit Scattered discrete areas of anthracosis throughout the lungs

(Ryder-Davies & Hime, 1972)

Liver damage, portal stenosis and elevated levels of alkaline phosphatase

Orangutan, *Pongo pygmaeus* male, 14 years old All long bones of arms and legs, first, second and forth metacarpals and proximal phalanx of the first digit Sub-acute purulent bronchopneumonia, secondary to virus infection, *E. coli*

Zoo animal, U.K. Pelvis, bones of the skull and jaw

(Hime *et al.*, 1972)

**Black lemur, *Eulemur macaco macaco*
family group 2**

Zoo animal, North America

female 1, 3 years old	Mainly metaphyseal regions of tibiae, fibulae, radii, ulnae femora and tarsal bones Diaphyseal periostitis (Mild degeneration of articular cartilage, assumed secondary to the exostoses, mild synovitis)	Chronic interstitial nephritis, mild renal osteodystrophy, high levels of BUN and ALP
female 2, 27 years old	Mainly metaphyseal regions of femora, tibiae, fibulae and radii (Osteoarthritis of left stifle joint)	Chronic interstitial nephritis, high levels of ALP
female 3, 19 years old (Junge <i>et al.</i> , 1994)	Tibiae, fibulae, radii, ulnae femora, tarsal bones and phalanges of the first digit of the hind limbs	Chronic interstitial nephritis

**Black lemur, *Eulemur macaco macaco*
Family group 3**

Zoo animal, North America

female, adult	Mainly the distal portions of tibiae, fibulae and metatarsal bones	Membranoproliferative glomerulonephritis, high levels of BUN and ALP Diffuse opacity in a caudal diaphragmatic lung lobe; not detected during subsequent examinations
female, 8 years old	Mainly the distal portions of femora, tibiae, fibulae, radii and ulnae	Chronic interstitial nephritis
male, 11 years old (Junge <i>et al.</i> , 1994)	Mainly the distal portions of tibiae, fibulae and radius	Mild chronic interstitial nephritis, high BUN concentrations

Reptiles

Iguanid lizard, <i>Iguana iguana</i> female, adult (Chiodini & Nielsen, 1983)	All vertebrae posterior to the second coccygeal vertebrae (Sclerosis of the spine)	Metastatic calcification and urate nephropathy
---	---	--

Black and white tegu lizard, <i>Tupinambus teguixin</i>	All limbs, mainly forelimbs	-
(Divers & Mader, 2005)		

Ursidae		
Raccoon dog, <i>Procyon lotor</i> male, adult	Long bones and the phalanges	Pink firm nodule, 2cm in diameter in the caudal proportion of the middle lung lobe. Several smaller nodules present in the pancreas
Conservation and Research Center, USA		
(Joint pathology center, 2003)		
Raccoon dog, <i>Nyctereutes procyonides</i> female	Metacarpal, metatarsal and femorotibial joints, extending to the epiphysis and metaphysis of adjacent bones	Chronic bronchitis with pyogranulomatous lesions associated with <i>Nocardia</i> -like bacteria
Free-living, Japan		
	(Pre-existing metaphyseal bone was thinned and in some areas resorbed)	
	Degeneration of tibial articular cartilage and villous proliferation of the synovial membrane of the metacarpal joints)	
(Masegi <i>et al.</i> , 1994)		

DISCUSSION

This literature review shows a wide range of wild animal species diagnosed with secondary HOA. The name and definition of the syndrome has differed through history and consequently how it has been named in studies, which may make it challenging to retrieve all documented cases.

Even though digital clubbing was described over 2000 years ago by Hippocrates and has been reported from even older archeological findings, the exact pathogenesis remains unknown. A wide range of possible affecting factors have been discussed, including neural influence, circulatory changes, growth factors and cell activity.

Initially HOA was thought to be associated only with pulmonary diseases, which has influenced the earlier naming of the syndrome and thoughts on possible pathogenesis. Studies of human HOA have described hypoxia to be a factor of interest (Paton *et al.*, 1991; Silveira *et al.*, 2000; Atkinson & Fox, 2004). The presence of hypoxia seems to fit in with other hypotheses of the underlying pathogenesis of HOA. Induced by hypoxia the growth factors VEGF and PDGF can cause stromal and vascular changes in the periosteal tissue of the limbs

that precedes manifest HOA (Atkinson & Fox, 2004). The fact that VEGF and PDGF also are induced by platelet aggregation (Dickinson & Martin, 1987; Atkinson & Fox, 2004) supports the theory that elevated levels of growth factors are caused by a pulmonary shunt (Dickinson & Martin, 1987). However, hypoxia is not likely to be the only cause of secondary HOA, since diseases not associated with hypoxia are believed to be able to cause this syndrome such as; Crohn's disease, ulcerative colitis (Oppenheimer & Jones, 1982) and vascular graft infection (Ahrenstorf *et al.*, 2012).

Pulmonary and intestinal lesions are the most frequently reported changes associated with secondary HOA. These organ systems have macrophages in large numbers, which can support the hypothesis that chronic activation of macrophages may induce clubbing (Toovey & Eisenhuer, 2010). The immune system varies between individuals; hence the macrophages are activated to a variable extent. This may also explain the difference in severity among individuals with secondary HOA. However, no studies have clearly proven the exact mechanism behind secondary HOA and the suggested causes are only hypotheses.

The pathogenesis of secondary HOA remains elusive.

Secondary HOA has been presented as mainly single cases in a wide range of species. The disease clearly affects a variety of animal species, not only domestic animals. Even though the lesions in animals sometimes differ compared to the lesions described in humans, there is a clear resemblance. The underlying diseases seen with secondary HOA in wild animals follow the same pattern as in humans and domestic animals with thoracic neoplasms and chronic pulmonary infections as the most frequent lesions. The clinical manifestations of secondary HOA in wild animals differ greatly between individuals. The individual may show no clinical signs or become anorectic, depressed and having difficult to move due to stiffness and painful limbs. Noticeable is that a gibbon monkey was presented with no signs of pain (Ryder-Davies & Hime, 1972), whereas in human patients pain is a common feature of secondary HOA. This gibbon monkey is the single case, of secondary HOA in a wild animal species, reported with clear absence of pain. However, presence or absence of pain has not been evaluated or mentioned in most case descriptions.

A lizard diagnosed with HOA was presented with periosteal proliferation of vertebrae. This is an uncommon site of periosteal bone proliferation and may have been induced due to neurogenic damage associated with trauma and increased blood flow during regeneration of the tail. The tail in the lizard does in many ways resemble a limb being very muscular, well vascularized and large in relation to body size (R J Chiodini, 1983).

Apart from bacterial and fungal infection, also parasites can cause lesions. *Spirocerca* sp. have, in dogs, been reported in association with secondary HOA. *Spirocerca lupi* is an esophageal worm which can be found in canines and has also been reported in large carnivores in tropical and subtropical environments, for instance, hyenas, *Crocuta crocuta*, cheetah, *Acinonyx jubatus* (Murray *et al.*, 1964) and jackals, *Canis mesomelas* (Brodey *et al.*, 1977). So there is probably potential for this or other parasites to cause HOA in wild animals.

In conclusion, secondary HOA shows similarities across species in regard to clinical symptoms and pathology of the skeleton. It is seen in combination with other, often thoracic, lesions, suggesting a common, but still not established pathogenesis in humans and animals, including wild animals.

REFERENCES

- Ahrenstorf, G., Witte, T., Schmidt, R. E., Rihl, M., Pichlmaier, M. A. & Rosenthal, H. (2012). Unilateral hypertrophic osteoarthropathy in a patient with a vascular graft infection. *Journal of Clinical Rheumatology*, 18(6), pp 307–309.
- Atkinson, S. & Fox, S. B. (2004). Vascular endothelial growth factor (VEGF)-A and platelet-derived growth factor (PDGF) play a central role in the pathogenesis of digital clubbing. *The Journal of Pathology* [online], 203(2), pp 721–728. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/path.1565/abstract>. [Accessed 2015-02-24].
- Ball, N. (1929). Fall von multipler Exostosenbildung bei einem Hirsche. *Archiv fuer wissenschaftliche praktische Tierheilkunde*, 60, p 235–.
- Ball, V. & Lombard, C. (1926). *Bull. Acad. Méd.*, 95(16).
- Bamberger, E. (1891). Über Knochenveränderungen bei chronischen Lunger- und Herzkrankheiten. *klin Méd.*, (93).
- Bamberger, E. *Wien Klin Wochenschr.* 1889(2), pp 226–230.
- Brodey, R. S. (1971). Hypertrophic osteoarthropathy in the dog: a clinicopathologic survey of 60 cases. *Journal of the American Veterinary Medical Association*, 159(10), pp 1242–1256.
- Brodey, R. S., Thomson, R. G., Sayer, P. D. & Eugster, B. (1977). Spiroceca lupi infection in dogs in Kenya. *Veterinary Parasitology* [online], 3(1), pp 49–59. Available from: <http://www.sciencedirect.com/science/article/pii/0304401777900073>. [Accessed 2015-02-18].
- Bush, M., James, A. E., Montali, R. J., Sauer, R. M., Heller, R. H. & Gray, C. W. (1974). Hypertrophic Pulmonary Osteoarthropathy in a Lioness (Panthera Leo). *Veterinary Radiology* [online], 15(2), pp 84–90. Available from: <http://onlinelibrary.wiley.com/doi/10.1111/j.1740-8261.1974.tb00688.x/abstract>. [Accessed 2015-02-16].
- Chiodini, R. J. & Nielsen, S. W. (1983). Vertebral osteophytes in an iguanid lizard. *Veterinary Pathology*, 20(3), pp 372–375.
- CLUBBING AND HYPERTROPHIC OSTEOARTHROPATHY. : Medicine.* [online] (LWW). Available from: http://journals.lww.com/md-journal/Fulltext/1942/09010/CLUBBING_AND_HYPERTROPHIC_OSTEOARTHROPATHY_2.aspx. [Accessed 2015-02-24].
- Cooper, G. W. & Hou, X. P. (1988). The effects of prostaglandin E1 on megakaryocyte proliferation in vitro. *Advances in Experimental Medicine and Biology*, 241, pp 217–224.
- Curtis, C., Dart, A., Rawlinson, R. & Hodgson, D. (1997). Hypertrophic osteopathy in an alpaca. *Australian Veterinary Journal* [online], 75(1), pp 61–62. Available from: <http://onlinelibrary.wiley.com/doi/10.1111/j.1751-0813.1997.tb13834.x/abstract>. [Accessed 2015-02-18].
- Davidson, C. S. (1984). *Medicine: An Illustrated History.* By Albert S. Lyons and R. Joseph Petrucelli, II. 616 pp. New York: Harry N. Abrams, 1978. *Hepatology* [online], 4(6), pp 1264–1264. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/hep.1840040633/abstract>. [Accessed 2015-02-23].
- DeSanto, J. (1997). Hypertrophic osteopathy associated with an intrathoracic neoplasm in a rabbit. *Journal of the American Veterinary Medical Association*, 210(9), pp 1322–3.
- Van De Watering, C. C., Zwart, P. & Barker, J. (1972). Cavernous tuberculosis of the lungs and secondary hypertrophic osteoarthropathy in a Siberian tiger (Panthera tigrus). *Journal of Small Animal Practice* [online], 13(6), pp 321–327. Available from: <http://onlinelibrary.wiley.com/doi/10.1111/j.1748-5827.1972.tb06852.x/abstract>. [Accessed 2015-02-18].

- Dickinson, C. J. & Martin, J. F. (1987). MEGAKARYOCYTES AND PLATELET CLUMPS AS THE CAUSE OF FINGER CLUBBING. *The Lancet* [online], 330(8573), pp 1434–1435. Available from: <http://www.sciencedirect.com/science/article/pii/S0140673687911329>. [Accessed 2015-02-24].
- Divers, S. J. & Mader, D. R. (2005). *Reptile Medicine and Surgery*. Elsevier Health Sciences. ISBN 141606477X.
- Elewaut, D. (2005). Kelley's Textbook of Rheumatology, 7th edition (in 2 volumes). Edited by E. D. Harris Jr, R. C. Budd, G. S. Firestein et al. Elsevier Saunders, 2004. 1916 pp. ISBN 0721601413. *Rheumatology* [online], 44(4), pp 566–566. Available from: <http://rheumatology.oxfordjournals.org/content/44/4/566>. [Accessed 2015-02-23].
- Ferguson, N. M., Lévy, M., Ramos-Vara, J. A., Baird, D. K. & Wu, C. C. (2008). Hypertrophic Osteopathy Associated with Mycotic Pneumonia in Two Juvenile Elk (*Cervus Elaphus*). *Journal of Veterinary Diagnostic Investigation* [online], 20(6), pp 849–853. Available from: <http://vdi.sagepub.com/content/20/6/849>. [Accessed 2015-02-18].
- Ferrara, N. (2004). Vascular Endothelial Growth Factor: Basic Science and Clinical Progress. *Endocrine Reviews* [online], 25(4), pp 581–611. Available from: <http://press.endocrine.org/doi/full/10.1210/er.2003-0027>. [Accessed 2015-02-24].
- Ferreira, E. & Camões, I. (2013). Hypertrophic osteoarthropathy and congenital heart disease: this is not casual. *BMJ Case Reports* [online], 2013, p bcr2013009392. Available from: <http://casereports.bmj.com/content/2013/bcr-2013-009392>. [Accessed 2015-02-17].
- Flayell, G. (1956). REVERSAL OF PULMONARY HYPERTROPHIC OSTEOARTHROPATHY BY VAGOTOMY. *The Lancet* [online], 267(6911), pp 260–262. Available from: <http://www.sciencedirect.com/science/article/pii/S0140673656911862>. [Accessed 2015-02-24].
- Ginsburg, J. (1963). Hypertrophic pulmonary osteoarthropathy. *Postgraduate medical journal* [online], 39(457), p 639. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2482609/>. [Accessed 2015-02-18].
- Guyot, H., Sandersen, C. & Rollin, F. (2011). A case of hypertrophic osteoarthropathy in a Belgian blue cow. *The Canadian Veterinary Journal. La Revue Vétérinaire Canadienne*, 52(12), pp 1308–1311.
- Harada, S. I., Nagy, J. A., Sullivan, K. A., Thomas, K. A., Endo, N., Rodan, G. A. & Rodan, S. B. (1994). Induction of vascular endothelial growth factor expression by prostaglandin E2 and E1 in osteoblasts. *Journal of Clinical Investigation* [online], 93(6), p 2490. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC294462/>. [Accessed 2015-03-01].
- Hime, J., Keymer, I. & Appleby, E. (1972). Hypertrophic pulmonary osteoarthropathy in an orang-utan (*Pongo pygmaeus*). *Veterinary Record.*, 91(14), pp 334–7.
- Hoyo, S., Fujita, J., Yamadori, I., Ezaki, T., Watanabe, S., Yamanouchi, H., Miyawaki, H., Yamaji, Y., Nishioka, M. & Takahara, J. (1997). Hepatocyte growth factor and digital clubbing. *Internal Medicine (Tokyo, Japan)*, 36(1), pp 44–46.
- Huang, C.-H., Jeng, C.-R., Lin, C.-T. & Yeh, L.-S. (2010). Feline Hypertrophic Osteopathy: A Collection of Seven Cases in Taiwan. *Journal of the American Animal Hospital Association* [online], 46(5), pp 346–352. Available from: <http://www.jaaha.org/doi/abs/10.5326/0460346>. [Accessed 2015-02-18].
- HYPERTROPHIC OSTEOPATHY ASSOCIATED WITH RENAL GOUT IN A GREEN IGUANA,** *Iguana iguana*. [online]. Available from: <http://arav.conferencespot.org/54999-arav-1999-1.53493/1999-1.53596/f-019-1.53684/a-171-1.53694?qr=1>. [Accessed 2015-03-13].
- Joint pathology center (2003). . Available from: <http://www.askjpc.org/wsc/wsc/wsc02/02wsc23.pdf>. [Accessed 2015-03-17].
- Joint pathology center (2006). . Available from: <http://www.askjpc.org/wsc/wsc/wsc06/06wsc03.pdf>. [Accessed 2015-03-17].
- Jp, L., Gp, C. & L, G. (1992). Hypertrophic osteopathy in three horses and a pony. *Journal of the American Veterinary Medical Association* [online], 201(12), pp 1900–1904. Available from: <http://europepmc.org/abstract/med/1483912>. [Accessed 2015-02-23].
- Junge, R., Mehren, K., Meehan, T. & Crawshaw, G. (1994). PERIARTICULAR HYPEROSTOSIS AND RENAL-DISEASE IN 6 BLACK LEMURS OF 2 FAMILY GROUPS. *Journal of the American Veterinary Medical Association*, 205(7), p 1024–.

- Kaleo Ede, D. M. (2008). Hypertrophic osteoarthropathy in the hepatopulmonary syndrome. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases*, 14(4), pp 230–3.
- Kenny, D. E., Getzy, D. M., Eller, J. L. & Morgan, T. (1997). Hypertrophic osteoarthropathy in a blesbok (*Damaliscus dorcas phillipsi*). *Journal of Zoo and Wildlife Medicine* [online], pp 319–324. Available from: <http://www.jstor.org/stable/20095665>. [Accessed 2015-02-18].
- Klippel, J. H., Stone, J. H., Crofford, L. eslie J. & White, P. H. (2008). *Primer on the Rheumatic Diseases*. Springer Science & Business Media. ISBN 9780387685663.
- Ladds, P. (2009). *Pathology of Australian Native Wildlife*. Csiro Publishing. ISBN 9780643099401.
- Ladds, P. W. Pathology of Macropodes. Available from: <http://www.arwh.org/sites/default/files/files-uploads/18%20Pathology%20of%20macropods.pdf>. [Accessed 2015-03-17].
- Madson, D. M., Loynachan, A. T., Kariyawasam, S. & Opriessnig, T. (2009). Systemic *Conidiobolus incongruus* infection and hypertrophic osteopathy in a white-tailed deer (*Odocoileus virginianus*). *Journal of Veterinary Diagnostic Investigation: Official Publication of the American Association of Veterinary Laboratory Diagnosticians, Inc*, 21(1), pp 167–170.
- Marie, P. De l'osteo arthropathie hypertrophiante pneumonique. *Rév. Méd. Paris.*, 1890(10), pp 1–36.
- Martinez-Lavin, M., Hochberg, M. & Silman AJ. (2007). Hypertrophic oteoarthropathy. *Rheumatology*. 4th Ed. Mosby.
- Masegi, T., Yanai, T., Sakai, T., Matsumoto, C., Yamazoe, K., Nukaya, A., Kunimune, Y. & Ueda, K. (1994). Hypertrophic Pulmonary Osteoarthropathy in a Raccoon Dog (*Nyctereutes procyonoides*) with Chronic Pulmonary Inflammatory Lesions. *Journal of Wildlife Diseases* [online], 30(4), pp 612–615. Available from: <http://www.bioone.org/doi/abs/10.7589/0090-3558-30.4.612>. [Accessed 2015-02-18].
- Masson, M., Molnár, E., Donoghue, H. D., Besra, G. S., Minnikin, D. E., Wu, H. H. T., Lee, O. Y.-C., Bull, I. D. & Pálfi, G. (2013). Osteological and Biomolecular Evidence of a 7000-Year-Old Case of Hypertrophic Pulmonary Osteopathy Secondary to Tuberculosis from Neolithic Hungary. *PLoS ONE* [online], 8(10), p e78252. Available from: <http://dx.doi.org/10.1371/journal.pone.0078252>. [Accessed 2015-02-23].
- Mitlak, B. H., Finkelman, R. D., Hill, E. L., Li, J., Martin, B., Smith, T., D'Andrea, M., Antoniades, H. N. & Lynch, S. E. (1996). The effect of systemically administered PDGF-BB on the rodent skeleton. *Journal of Bone and Mineral Research* [online], 11(2), pp 238–247. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/jbmr.5650110213/abstract>. [Accessed 2015-02-24].
- M Martínez-Lavín, M. M.-C. (1993). Hypertrophic osteoarthropathy: consensus on its definition, classification, assessment and diagnostic criteria. *The Journal of rheumatology*, 20(8), pp 1386–7.
- Murray, M., Campbell, M. H. & Jarrett, W. H. F. (1964). *Spirocerca lupi* in a cheetah. *African Journal of Ecology* [online], 2(1), pp 164–164. Available from: <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2028.1964.tb00209.x/abstract>. [Accessed 2015-03-02].
- O Epstein, A. B. A. (1979). Hypertrophic hepatic osteoarthropathy. Clinical, roentgenologic, biochemical, hormonal and cardiorespiratory studies, and review of the literature. *The American journal of medicine*, 67(1), pp 88–97.
- Oppenheimer, D. A. & Jones, H. H. (1982). Hypertrophic osteoarthropathy of chronic inflammatory bowel disease. *Skeletal Radiology* [online], 9(2), pp 109–113. Available from: <http://link.springer.com/article/10.1007/BF00360493>. [Accessed 2015-02-23].
- Paton, J. Y., Bautista, D. B., Stabile, M. W., Waldman, A. E., Nassar, A. G., Platzker, A. C. & Keens, T. G. (1991). Digital clubbing and pulmonary function abnormalities in children with lung disease. *Pediatric Pulmonology*, 10(1), pp 25–29.
- Rj, L., Aj, G., Aa, M., Ww, W., Al, H. & Pd, K. (1978). Relationships among digital clubbing, disease severity, and serum prostaglandins F2alpha and E concentrations in cystic fibrosis patients. *The American review of respiratory disease* [online], 117(4), pp 639–646. Available from: <http://europepmc.org/abstract/med/646216>. [Accessed 2015-03-01].
- Ryder-Davies, P. & Hime, J. M. (1972). Hypertrophic osteoarthropathy in a gibbon (*Hylobates lar*). *The Journal of Small Animal Practice*, 13(11), pp 655–658.

- Salyusarenko, M., Peeri, D., Bibring, U., Ranen, E., Bdoah-Abram, T. & Aroch, I. (2013). Hypertrophic Osteopathy: a Retrospective Case Control Study of 30 Dogs. *Front Cover-The himalayan* [online], 68(3), p 3. Available from: <http://isrvma.org/ImageToArticle/Files/DECEMBER%202013%20EN.pdf#page=9>. [Accessed 2015-02-18].
- Sarkar, M., Mahesh, D. & Madabhavi, I. (2012). Digital clubbing. *Lung India* [online], 29(4), p 354. Available from: <http://www.lungindia.com/text.asp?2012/29/4/354/102824>. [Accessed 2015-02-17].
- Scaldaferri, F., Vetrano, S., Sans, M., Arena, V., Straface, G., Stigliano, E., Repici, A., Sturm, A., Malesci, A., Panes, J. & others (2009). VEGF-A links angiogenesis and inflammation in inflammatory bowel disease pathogenesis. *Gastroenterology* [online], 136(2), pp 585–595. Available from: <http://www.sciencedirect.com/science/article/pii/S0016508508017319>. [Accessed 2015-03-01].
- Schulze, C., Prejawa, T. & Paulick, D. (2005). [Case report: Hypertrophic osteopathy in roe deer (*Capreolus capreolus*)]. *DTW. Deutsche tierärztliche Wochenschrift*, 112(10), pp 393–394.
- Silveira, L. H., Martinez-Lavin, M., Pineda, C., Fonseca, M. C., Navarro, C. & Nava, A. (2000). Vascular endothelial growth factor and hypertrophic osteoarthropathy. *Clinical and experimental rheumatology* [online], 18(1), pp 57–62. Available from: <http://www.clinexprheumatol.org/article.asp?a=1557>. [Accessed 2015-02-24].
- Toovey, O. T. R. & Eisenhauer, H. J. (2010). A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. *Medical Hypotheses* [online], 75(6), pp 511–513. Available from: <http://www.sciencedirect.com/science/article/pii/S0306987710002379>. [Accessed 2015-02-17].
- Uppal, S., Diggle, C. P., Carr, I. M., Fishwick, C. W. G., Ahmed, M., Ibrahim, G. H., Helliwell, P. S., Latos-Bieleńska, A., Phillips, S. E. V., Markham, A. F., Bennett, C. P. & Bonthonron, D. T. (2008). Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. *Nature Genetics* [online], 40(6), pp 789–793. Available from: <http://www.nature.com/ng/journal/v40/n6/full/ng.153.html>. [Accessed 2015-02-23].
- U W Längle, S. B. (1994). Hypertrophic osteopathy in rats following chronic administration of SDZ MNS 949, an isoquinoline. *Experimental and toxicologic pathology : official journal of the Gesellschaft für Toxikologische Pathologie*, 45(8), pp 473–9.
- Wayne, J. & Nicholson, V. (1999). Hypertrophic osteopathy and pneumonia in a macropod. *Australian Veterinary Journal* [online], 77(2), pp 98–99. Available from: <http://onlinelibrary.wiley.com/doi/10.1111/j.1751-0813.1999.tb11676.x/abstract>. [Accessed 2015-03-15].
- Wilton, G. S. & Graesser, F. E. (1967). Hypertrophic pulmonary osteoarthropathy in a mink. *The Canadian Veterinary Journal* [online], 8(3), pp 77–78. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1696776/>. [Accessed 2015-03-13].
- Yao, Q., Altman, R. D. & Brahn, E. (2009). Periostitis and Hypertrophic Pulmonary Osteoarthropathy: Report of 2 Cases and Review of the Literature. *Seminars in Arthritis and Rheumatism* [online], 38(6), pp 458–466. Available from: <http://www.sciencedirect.com/science/article/pii/S0049017208001200>. [Accessed 2015-02-17].