Title: Hereditary Multiple Exostoses: A comprehensive examination of a 4 year old Dutch Warmblood male with maternal links to HME in the 1st and 2nd generations. Case Study

Key Words: Hereditary multiple exostoses (HME), Skeleton, Cartilage, Axial, Appendicular.

Abstract

1. Introduction

Hereditary Multiple Exostoses (HME) is a distinct skeletal disorder reported in humans, dogs, cats, lions, lizards, cattle and horses. The synonyms in current literature include; Osteogenic disease; Chondral osteogenic dysplasia; Chondral osteoma; Dyschondroplasia; Deforming chondrodysplasia; Multiple hereditary osteochondromata; Multiple cartilaginous exostoses or Exostosis dysplasia [1]. Primarily, HME in horses affects endochondral bones during skeletal development and is often seen at birth. Gross skeletal presentation can predominantly be seen in the ribs, scapula and limbs (Figure 1), with lesions appearing as cartilage capped spongy chondro-osseous growths [2].

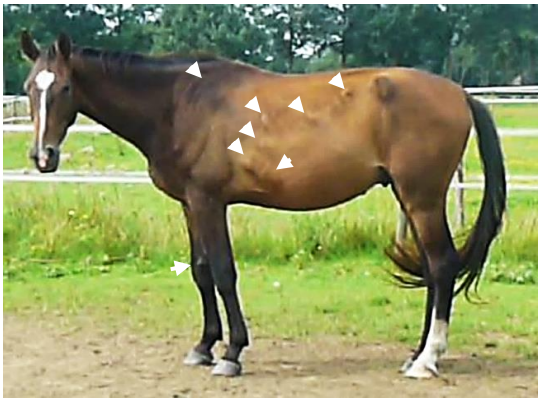

Figure 1. Four year old Dutch Warmblood male with HME of the ribs, scapular and right foreleg arrowed.

Familial relationships have previously been reported in the horse and human; one male line was identified in a Utah State University study in horses, and in humans, male and female lineage identified [2,3]. Diagnosis in horses is via radiographic evidence differentiating an Osteochondroma from HME, however in humans, radiographic evidence requires further diagnostic support [4]. Whereby in humans, HME is autosomal dominant with most displaying a mutation at the EXT-1 or EXT-2 genes; hence genetic diagnosis differentiates HME from other skeletal disorders such as metachondromatosis [5].

The clinical, gross and microscopic appearance of HME in horses resembles those in humans, however in the horse, lesions are clearly noted in most from birth,s with further lesions becoming obvious during periods of active skeletal maturation [2]. The lesions appear as

raised hardened structures beneath the skin and can cause skeletal deviation dependent on location in either the axial or appendicular skeleton [2,4,5]. Further complications arise when the lesions exert pressure on surrounding structures, such as tendons, nerves and some visceral organs [2]. This case study reports the findings of 6 horses with a maternal link over 17 years of investigations.

2. Material Methods

No horses were euthanised for the purpose of this case study.

2.1 Background History

In 1998, a 4 year old Dutch warmblood mare (M1), with show jumping ability, was examined for pre-purchase and bought with the purpose of a competitive show jumping career. In 2000, at the age of 6, M1 was retired from show jumping with tendon pathology. Over the next 13 years she produced 8 Dutch Warmblood foals. Three from eight presented with skeletal disorders; 2 offspring diagnosed HME and 1 diagnosed Osteochondroma; Foal No.1 (F1) female sired by A; Foal No.2 (F2) female sired by B; Foal No.8 (F8) male sired by C. F3 to F7 displayed no remarkable lesions and were kept > 1 year of age before sold.

At birth, F1 and F8 presented with bony exostoses 1st Phalanx (PI), F2 was clear. Within the first year postpartum, F1 developed further lesions on the limbs and F8 developed lesions on the limbs and ribs. At 1½ years, F8 was castrated and thereafter the lesions became noticeably worse over the limbs and ribs.

Radiographic regions of M1; F1; F2; F8 post mortem are reported in Table 1.

Table 1. Radiographic regions of F1, F2 and F8 (post mortem).

Radiographic Regions	Age	AP - Carpus	AP - Tarsus	AP - Inter phalangeal	AP - PI, PII, PIII	AP- Carpus/ Distal Radius	AP - Tarsus/ Distal Tibia	AX - Ribs	Other
M1 (n=12)	4		4	4	4				
F1 (n=24)	4mths & 5	2	6	6	3	2		-	5
F2 (n=18)	4		4	4	4		2	-	4
F8 (n=21 PM)	4	3	2				1	10	5

Key: AP – Appendicular; AX – Axial; P – Phalanx; PM – post mortem.

F1 produced 3 foals prior to euthanasia with chronic carpal lameness. Foal No.1(FF1) female sired by Y; Foal No.2 (FF2) male sired by Z; Foal No.3 (FF3) sired by Y. The maternal links are noted in Figure 2.

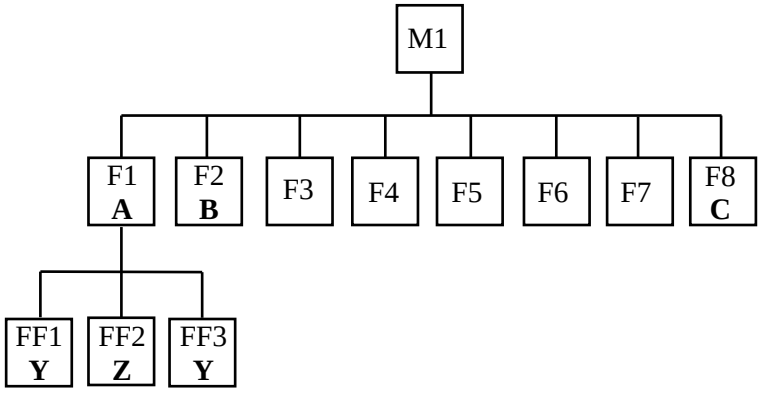

Figure 2. The 1st and 2nd generations of M1 with bold letters denoting sire.

All horses produced by M1 were bred at the same facility.

2.2 Methodology

Diagnostic reports and radiographs for M1, F1 and F2 were acquired retrospectively and post mortem for F8.

F8 was euthanised at 4 due to the extensive number of rib lesions. The visceral organs were removed, and soft tissue structures resected. Histological samples were resected from the lateral distal mid shaft of the right 6th sternal rib, packaged in a biological category B sealed bag and delivered directly to the pathology laboratory for histological analysis. Whereby hematoxylin-eosin staining was performed on the samples according to standard operating instructions.

Thereafter, the bones of F8 were macerated to reveal the extent of HME in the skeleton. Each bone was comprehensively examined, documented and compared to corresponding radiographs.

FF1, FF2 and FF3 were externally examined and palpated by veterinarians with no radiographs. Communication with the owner could only provide a verbal report for FF1, FF2 and FF3 with accompanying juvenile photographs.

3. Results

Radiographic results confirming Osteochondroma and HME in F1, F2 and F8 post mortem can be seen in Table 2.

Table 2. Radiographic regions of F1, F2 and F8 confirming Osteochondroma and HME.

Radiographic Regions	Age	AP - Carpus	AP - Tarsus	AP - Inter phalangeal	AP - PI, PII, PIII	AP- Carpus/ Distal Radius	AP - Tarsus/ Distal Tibia	AX - Ribs	Other
M1 (n=12)	4		4	4	4				
F1 (n=24)	4mths & 5	2	6	6	3	**2**		-	5
F2 (n=18)	4		4	4	4		**2***	-	4
F8 (n=21 PM)	4	**3**	2				**1**	**10**	**5**

Bold denotes HME; ***** denotes Osteochondroma
Key: AP – Appendicular; AX – Axial; P – Phalanx; PM – post mortem.

In F1, HME was noted in the distal anterior surface of the right foreleg. In F2, osteochondromas were noted in the distal left and right tibia.

In F8's post mortem examination, HME was present on 106/205 bones; the axial skeleton exhibited the maximum number of HME lesions; Hyoid apparatus (n=7/8); Cervical Vertebrae (n=7/7); Thoracic vertebrae (n=18/18); Lumbar vertebrae (n=6/6); Sacrum (n=1/1); Caudal vertebrae (n=1/18); Ribs (n=36/36); Sternum (n=1/1). The appendicular skeleton; Left foreleg (n=9/21), Carpals (ulna); Right foreleg (n=10/21), Carpals (2nd, Intermediate and Radial); Left hindleg (n=4/20); Right hindleg (n=4/20); Pelvis left and right (n=2/2). The extent of HME in F8 can be seen in Figure 3.

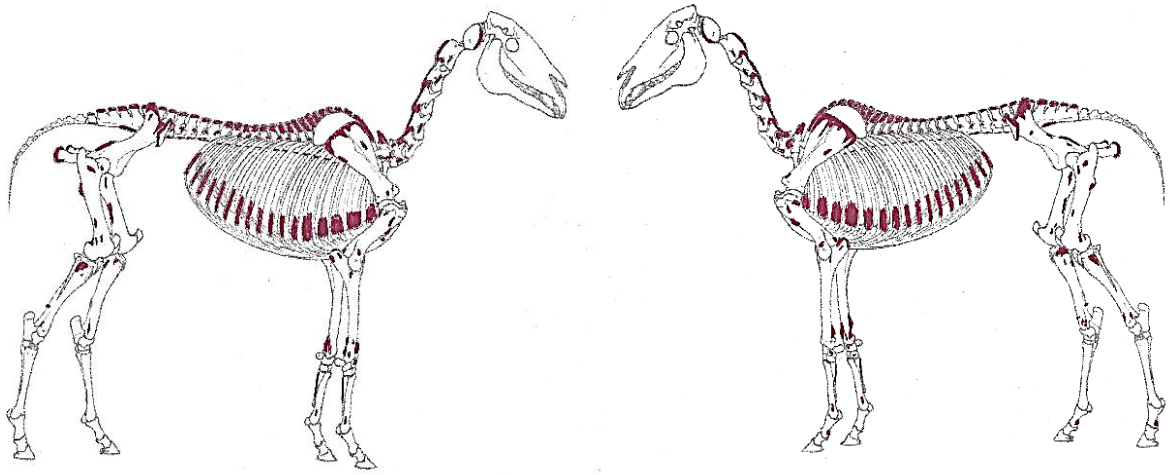

Figure 3. Left and right skeletal view of F8 presenting the location and extent of HME in red.

The HME in F8 was quite remarkable in the axial skeleton and most notably in areas of muscle attachment, including the diaphragm. The lesions were varied from simple raised columns (Figure 4) to bulbous exostoses up to 20cms in length (Figures 5).

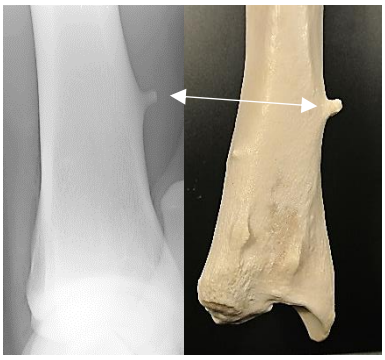

Figure 4. The HME lesion of the right tibia in F8. Note the exostoses depicted in the radiograph corresponds with the post mortem equivalent arrowed.

The medial aspect of the ribcage displayed lesions pressing against visceral organs Figure 5.

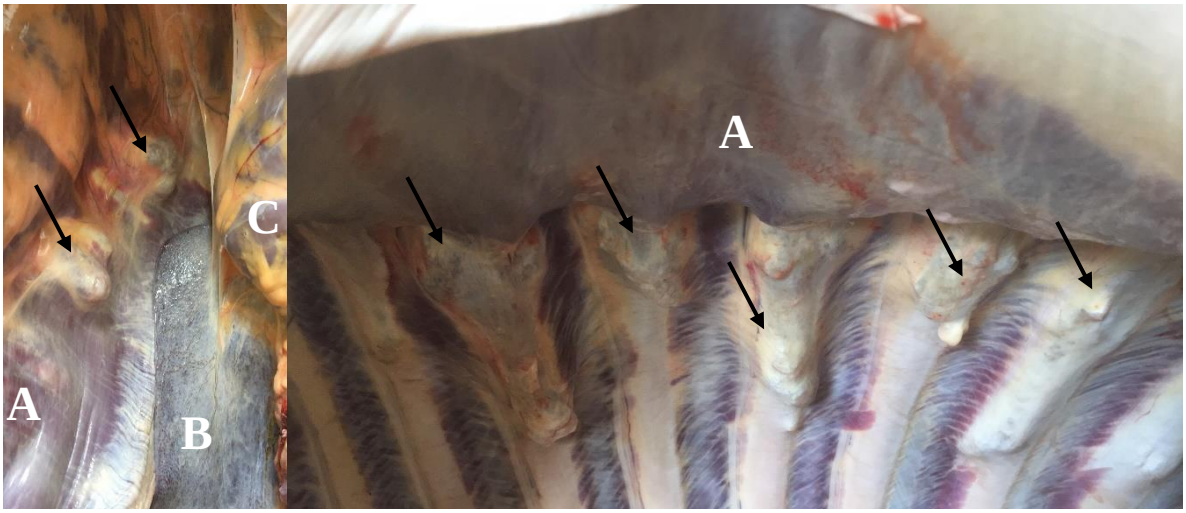

Figure 5. The view of HME (arrowed) from inside the ribcage of F8. Diaphragm A; Spleen B and Kidney C.

Histological analysis of the lesion in F8 reported the tissue of both samples works with a cancellous bone with thin, well-differentiated mature trabeculae and haematopoietically active bone marrow. Superficially, the sample has a continuous layer of hyaline articular cartilage. The larger sample displays multiple, partly veiled benign cartilage islands. There are also fissures, necrosis and cyst formation. A thin layer of collagenous connective tissue covered the top of the sample. Diagnosis: Heritable Multiple Exostoses.

FF1, FF2 and FF3 developed sub dermal rib lesions by 1 and limb lesions by 4, as per F8. FF2 developed axial deviations after 2.

4. Discussions

Heritability of HME has been previously reported in the horse and human [1-3]. In one study, a relationship was established between a 42 year old woman with no history or signs of HME, however, her brother and daughter were affected. From the cited study, it was extrapolated that HME could be carried with no evidence of the disease [3]. These findings concur with those pertaining to the one male line identified in the Utah State University study; whereby, the unaffected stallion produced 15 HME horses in the 1st generation with 6 in the 2nd generation. In the current study, whereby radiographs of MI at 4 years of age displayed no HME, it also follows the familial line with 2/8 foals produced by M1 displaying exostoses at birth and 3/3 in the 2nd generation displaying exostoses of the ribs by 1. Although in humans, research indicates a greater transmission in the male line than the female [1], there were no common sires found in the familial line in this study.

The presentation of HME is representational between the horse and human, including microscopic level [2] and concur with the histological report of F8. Although, no scientific evidence could be found by this author that cervical or hyoid bones exhibit HME, F8 presented with extensive HME on both. This is not consistent with human research and therefore deviates from current literature and would be regarded as a new finding. One case study worth mentioning is the report of 2 growth hormone (GH) deficient children; they were first diagnosed with traditional blood tests for GH; the first presented with solitary osteochondromas in familial lines and the second with HME in familial lines. Both underwent Magnetic Resonance Imaging that produced identical findings; a reduction in size of the pituitary gland and thickening of the pituitary stalk [6]. Even though a combined HME and osteochondroma familial line has not been previously established, it is worth noting that F2 presented with osteochondromas, and 2 siblings by different sires displayed HME - F1 and F8.

In humans it has been reported that HME is rarely found in carpals, tarsals and or on those bones of the skull; that it interferes with tendons, ligaments and musculature by exerting pressure on soft tissue structures creating contracture of joints; that bony exostoses have created curvatures and deviations such as scoliosis of the spine; and that visceral organs have also been subject to internal exostoses [1-3]. These all concur with the current findings in this study, except for the carpal lesions. F8 presented with bilateral carpal lesions; the most

extensive of which was noted on the right carpus, this coincided with the lesion on the distal radius thus altering his posture (Figure 1). F8 also exhibited pressure of the visceral organs, notably the diaphragm and spleen in Figure 5, and scoliosis or axial malformation was reported in FF2 post 2 years of age. These presentations are all accepted as clinically relevant in both species, although only radiographically diagnosed in horses.

Of further interest is the presentation of exostoses on P1 at birth; as noted in this study in F1 and F8. In horses, HME is most often present at birth, similarly in humans, [1-3]. Although in humans, presentation can be noted postpartum up to 12 years of age with the adage that stature is often affected [1-3, 5]. No horses in this study displayed a decrease in stature due to HME and although F2 presented with 2 osteochondromas at 4 in bilateral tibias, no further lesions were noted thereafter, nor a decrease in stature. Furthermore, osteochondromas have been reported in the distal tibia, with no breed predilection, in many, surgical intervention of the osteochondroma has resolved the associative issues, and presentation can be bilateral as reported in the current study [7].

5. Conclusion

HME is a rare skeletal condition in horses, with no known treatment and diagnosis is reliant on radiographs. As both HME and osteochondroma are autosomal dominant skeletal disorders and one study identified GH deficiency via blood tests coinciding with pituitary gland abnormalities in a HME patient and a osteochondroma patient [6], it therefore could be postulated that blood tests may provide a further diagnostic tool in HME subjects. Early diagnosis in suspect horses could provide the owner/breeder with a clear diagnosis prior to essential decision making pertaining to training and breeding.

6. References

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