Rapid development of secondary hyperparathyroidism and fibrous osteodystrophy in a juvenile orangutan

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Abstract This study presents a probable case of rapidly-developed fibrous osteodystrophy and secondary hyperparathyroidism in a juvenile wild-caught zoo orangutan, *Pongo pygmaeus*. Cases of this metabolic disease, associated with captivity in primates, are underreported in non-human Hominidae, and none to the extent of postcranial afflictions. We present the first described case of these metabolic pathologies of a great ape at both the cranial and skeletal levels.

Keywords *metabolic disease, orangutan, osteodystrophia fibrosa, zoo animal*

1. Introduction

The parathyroid glands are responsible for maintaining calcium homeostasis through the production of parathyroid hormone (PTH). In response to low circulating ionized calcium levels, PTH causes osteoclastic breakdown of bones, thereby increasing circulating ionized calcium (Fraser, 2009). When low levels of circulating ionized calcium result from a disruption of homeostatic mechanisms, vitamin D₃ deficiency and/or chronic kidney failure, secondary hyperparathyroidism can result (Selvi et al. 2009).

Fibrous osteodystrophy (also called osteodystrophia fibrosa or osteitis cystica fibrosa), which triggers hyperostotic distortion of cancellous bones, conjunctive tissue proliferation, and poor mineralization of bone, is one such product of secondary hyperparathyroidism (Ospina et al., 2014). This pathology has been demonstrated in wild-caught zoo animals whose dietary restrictions and unnatural housing conditions resulted in the development of metabolic diseases and frequent, premature deaths in the early 20th century (Junge et al., 2000; Farrell et al., 2015). An extensive literature search for great apes afflicted with these metabolic pathologies yielded two studies with five orangutan skulls (Scheidegger and Wendnagel, 1949 ; Röhrer-Ertl and Frey, 1987). We present the first described case of probable secondary hyperparathyroidism and fibrous osteodystrophy of a great ape at the skeletal level.

2. Case report

Specimen USNM 296650 is a skeletal-prepped, juvenile, male *Pongo pygmaeus* purchased in northern Borneo in August 1952. It was delivered by ship to the National Zoological Park in Washington, D.C., and died four months later. The incomplete skeleton was deposited at the National Museum of Natural History, Washington, D.C.

Superficially, the degree of dental eruption allows for an estimated age of 5–6 years, though its severe medical condition and periods of high stress may have delayed development. Long bone epiphyses are too diseased to be used as proxies for aging (Fig. 2). Autopsy records could not be obtained.

2.1 Cranial pathologies (Fig. 1)

The most obvious cranial manifestation of the underlying disease is the bilaterally-enlarged mandible and maxilla. Here, extensive osteoclastic resorption left the elements brittle and unable to enclose postcanine teeth. Swelling by means of non-neoplastic osteoclastomas, called brown tumors (Selvi et al., 2009), likely occurred in the cortical bone of the maxillofacial region during the process of bone replacement by fibrous tissue. Maxillary swelling extends upward from the alveolar margins to the frontal process, spanning the splanchnocranium. Spongy hyperostosis of the neurocranium is most evident in the parietal bones. The mandible exhibits

the most severe degree of de-ossification. Inflammation significantly increased and “bowed” the rami posteriorly and the coronoid processes are gone.

Figure 1 Computed Tomographic and photographic images of skull. Note the pitting of the skull secondary to bone loss. Scans and photos by D Hunt.

2.2 Postcranial pathologies (Fig. 2)

Postcranial elements are nearly equally afflicted, particularly in load-bearing elements. Porosity of the vertebrae increases caudally, as the first cervical vertebra is least affected. Sacral elements display porosity, though the coccyx is less affected. Scapulae are coral-like in structure with major breakdown of bone material and exposure of internal trabecular bone. Ribs are bent inwards at the shaft. Iliac are less damaged than the scapulae, though resorption is apparent; very minor in the ischia and pubis bones. All long bones suffered extensive loss of density. The left tibia exhibits a very slight, possibly pathological curvature. Surprising was the absence of obvious fractures sustained during life. Given the exceptionally fragile condition of its postcrania, the animal was likely predominantly sedentary and could not easily bear its own weight.

Figure 2 (A) USNM 296650 (B) severe deforming of the ribs with porosity of vertebral elements (C) tibiae and fibulae (D) humeri; Photos by D. Hunt.

3. Discussion

Though commonly documented in humans, metabolic diseases, including secondary hyperparathyroidism have been reported in a number of species, including captive nonhuman primates (Farrell et al. 2015). In the five published accounts on apes, the onset of disease and manifestations of observable symptoms were rapid, though cause of death could not be attributed directly to the diseases themselves (Scheidegger and Wendnagel, 1949 ; Röhrer-Ertl and Frey, 1987). These animals were also wild-caught and housed in captivity. Prior to the mid-twentieth century, many captive orangutans fell terminally ill to pneumonia, infections, and human-borne viruses – a result of meager housing conditions and a poor understanding of captive ape medical care (Ulmer 1966).

A comprehensive literature search on the disorders of captive primates became the basis for our suggested diagnosis. Two possible triggers of vitamin D deficiency and subsequent secondary hyperparathyroidism, insufficient exposure to direct sunlight and dietary restrictions (Fraser 2009), align with the orangutan's captive status. The extensive degree of bone damage and deformation exhibited in the juvenile orangutan coincides with its young age. The normal processes of apposition and resorption in the growing bones were disturbed by a reduction in calcium deposits and possibly the elevated stress associated with captivity. Cortical bone is especially vulnerable to osteoclastic bone resorption, which may explain the great severity in mandibular bone loss (Selvi et al. 2009).

Various pathologies with similar characteristics to nutritional hyperparathyroidism were considered in the differential diagnosis (Table 1). With consideration of age, trauma, and captive status that our recommendation is further supported.

Table 1. Diagnostic features considered in the differential diagnosis of USNM 296650.

Disease	Diagnostic characters
Chronic kidney disease ^{1,2}	The deterioration of renal function can trigger secondary hyperparathyroidism. High levels of the PTH are known to contribute to changes in bone remodeling from altered levels of calcium.
Grave's disease ³	Stress from captivity may contribute to inciting thyroid-autoimmunity (though no conclusive evidence has been found of Grave's disease among non-human apes).
Hungry bone syndrome ⁴	This syndrome is known for its persistent hypocalcemia, leading to high bone turnover intensified by PTH level suppression. It can result from vitamin D deficiency and has been documented in humans with primary hyperparathyroidism. It may include the presence of brown tumors.
Hyperparathyroidism – jaw tumor syndrome ⁵	A genetic syndrome in which hyperparathyroidism is typically caused by a benign or malignant tumor of the parathyroid gland. This can lead to ossifying fibromas in the jaw, most frequently in cheek teeth (premolar and molar) regions.
Juvenile Paget's disease ⁶	An autosomal recessive osteopathy that results from a deletion of the gene that encodes for osteoprotegerin. Produces accelerated-bone remodeling throughout the skeleton with a disorganization of the trabecular layout.
Ossifying Fibromas ⁵	An alternative hypothesis to the presence of maxillofacial brown tumors in the orangutan specimen; evidence of cheek teeth displacement, with mandibular and maxillary bone swelling. Ossifying fibromas are typically asymptomatic and not directly associated with any particular genetic mutations.
Osteoblastoma ⁶	An additional alternative hypothesis to the maxillofacial brown tumors. A very rare, benign bone tumor which, when localized in the jaw, can account for swelling and bone-cortex expansion.
Primary Hyperparathyroidism ²	A secretion of excess parathyroid hormone resulting in hypercalcaemia, whereby high calcium levels in the blood prevent normal osteoblastic repairs, resulting in possible bone loss.

1. Silver & Naveh-Many (2013); 2. Fraser (2009); 3. McLachlan et al. (2011); 4. Witteveen et al. (2013); 5. Wang et al. (2014); 6. Whyte et al. (2002); 6. Capodiferro et al. (2005)

4. Conclusion

The cranial and skeletal evidence described in this juvenile orangutan overwhelmingly demonstrates pathologic replacement of normal mineralized bone tissue with connective tissue. By comparing osseous pathologies seen in other species, the most likely diagnosis is secondary hyperparathyroidism and fibrous osteodystrophy. When conducting clinical investigations into metabolic diseases, confounders such as age and living conditions should be specifically considered, as the effects on growth-related bone processes in this specimen has demonstrated. Investigation of addition postcranial elements in a range of ages and species will be necessary to better understand the developmental upsets this metabolic disease plays in the process of bone growth among great apes.

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