

Historical Note**Pycnodysostosis: Toulouse-Lautrec's and Aesop's disease?**

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Among the several causes of short stature is pycnodysostosis, also known as "Toulouse-Lautrec's disease".^{1,2} Robert Weismann-Netter is credited with the first description of the disorder which later became known as pycnodysostosis.³ Only a few, however, know that pycnodysostosis was also possibly Aesop's disease⁴.

TOULOUSE-LAUTREC

Henri de Toulouse-Lautrec (1864-1901) was initially thought to have had osteogenesis imperfecta. However, following the description of pycnodysostosis as a new genetic skeletal dysplasia, Maroteaux and Lamy⁵ concluded that this was Toulouse-Lautrec's affliction (Figure 1). He, in fact, presented all the clinical features suggestive of this diagnosis, in addition to parental consanguinity. Toulouse-Lautrec had bone fragility leading to fractures with minor trauma, a receding chin and possibly open fontanelles, explaining the artist's insistence on wearing a hat most of the time².

Pycnodysostosis was often confused with cleidocranial dysplasia. Both disorders present with multiple Wormian bones and delayed closure of the cranial sutures, particularly the lambdoid and the sagittal. The

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ramus of the mandible is short and the angle lost, so that this bone is essentially straight and the jaw receding. Bones are fragile and frequent fractures may occur.

AESOP

Of striking resemblance to Henri de Toulouse-Lautrec (Figure 1) is the representation of Aesop on a 5th century B.C. cylix, presently displayed in the Vatican Museum (Figure 2). A freed slave from Samos, Aesop lived in the 6th century B.C. He was endowed with abundant discernment and wisdom and boasted a rich fund of old myths as well creating his own myths. His ugliness was reported by several ancient authors. Characteristic is the 450 B.C. cylix, now in the Vatican museum, where Aesop is depicted talking to a fox. H.J. Kaufmann (in a letter to the author dated Jan.16, 1973) speculatively suggested that Aesop's characteristics on the black-figured cylix bore the facial features of pycnodysostosis⁴.

Aesop is the world-renowned author of a large number of fables, i.e. short narratives making an edifying or cautionary point and often employing as characters animals that speak and act like human beings. The known facts about Aesop are that he was a Greek slave sold by Xanthus to Iadmon, a Samian, later murdered by Delphic priests because he denounced their greed (Aristophanes, *Vespae*⁶ 1446-8). Although a biography of Aesop may have existed already in the 5th century BC, a number of mythical biographies followed much later during Roman times. What has come down to us concerning him are numerous anecdotes about Aesop and his Samian master, the sage Xanthus, and accounts of Aesop's career as adviser in the



Figure 1. Toulouse-Lautrec (1864-1901). Printed by permission of Mosby Co and Dr. V.A. McKusick.

court of the Lydian King Croesus.

PYCNODYSTOSIS

Clinical data

Patients with pycnodysostosis (OMIM:265800) manifest skull deformity, short stature usually reaching a height of a less than 150cm, craniofacial disproportion due to underdeveloped facial bones and a prominence of the frontal and parietal bones, obtuse angle of the mandible, widening of the cranial sutures, persistence of the fontanels and delayed exfoliation



Figure 2. Aesop (6th century b.C.) as he appears on a 5th century b.C. cylix (Vatican Museum). Printed by permission of the Vatican Museum (Monumenti Musei e Gallerie Pontificie).

of deciduous teeth. Permanent teeth appear on schedule but may be malformed or malpositioned. Other features include a narrow, grooved palate. The clavicles are dysplastic with partial aplasia of the acromial ends. The terminal phalanges of the digits are short with acroosteolysis and wrinkling of the skin over the dorsal surfaces distally, and flattened nails. Radiographic examination shows an increased density of bone of the entire skeleton, osteosclerosis, delayed closure of cranial sutures, wormian bones, open fontanels and hypoplastic facial bones and sinuses. An obtuse mandibular angle and dental irregularities are present on skull films. There is tapering of the distal phalanges with absence of the unguis tufts and segmentation anomalies of the vertebrae. Long bone deformities due to fractures may be present ⁷.

Endocrine data

Soliman et al⁸ reported defective growth hormone secretion in response to provocation and low IGF-1 concentration in 5 out of 6 patients with pycnodysostosis. Growth hormone replacement in 2 boys succeeded in increasing IGF-1 concentration and improved the linear growth in these children. Normal sexual development, fertility, serum TSH, T4, cortisol, gonadotropins and testosterone were evidence against abnormalities of the hypothalamic-pituitary-gonadal axis.

Genetic data

By linkage analysis, Gelb and coworkers⁹ demonstrated, in an inbred Arab kindred reported previously by Edelson and co-workers¹⁰, that the pycnodysostosis gene (PYCD) is located on chromosome 1q21, also confirmed by Polymeropoulos¹¹. Thirteen of 16 affected individuals were homozygous for the D1S305 allele, which had been previously assigned to the pericentromeric region of chromosome 1. One year later, Gelb and co-workers¹², recognizing the fact that cathepsin K, a cysteine protease gene which is highly expressed in osteoclasts, maps in the same region as pycnodysostosis, studied possible mutations of the cathepsin K gene as causes of pycnodysostosis.

Pycnodysostosis patients had nonsense, missense and stop codon mutations of the gene. No immunologically detectable protein was found. A missense mutation ala277 to val inherited only from the father was identified by Gelb and coworkers¹³ as uniparental disomy for chromosome 1 in a patient with the features of pycnodysostosis. Therefore, Gelb et al¹² suggested that cathepsin K, being a major protease in bone resorption, a process mediated by osteoclasts, is characterized by solubilization of inorganic mineral and subsequent degradation of organic matrix, primarily type 1 collagen.

In fact, in pycnodysostosis, the number of osteoclasts is normal but the region of demineralized bone surrounding them is increased. Large, abnormal cytoplasmic vacuoles containing bone collagen fibrils were observed by ultrastructural examination. The conclusion is that although pycnodysostosis osteoclasts function normally in demineralizing bone, they do not adequately degrade the organic matrix.

CONCLUSION

Lesions on the human genome are the causes of the 4000 or so recognized inherited diseases. The incidence of genetic diseases in the population may indicate the duration of existence of the mutated genes in humanity. Very ancient mutations have the oppor-

tunity timewise to spread widely through population migrations. Therefore, the scarcity of the pycnodysostosis gene could indicate a relatively more recent mutation. Nonetheless, it is interesting to note that the resemblance of Aesop's characteristics to those of pycnodysostosis may support the speculation about the existence of the pycnodysostosis gene in ancient Greece.

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