Commentary

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Current research on pycnodysostosis

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Summary **Pycnodysostosis is a rare autosomal recessive disorder caused by an inactivating mutation in *cathepsin K* (*CTSK*) and characterized by dysmorphic facial features, a short stature, acroosteolysis, osteosclerosis with increased bone fragility, and delayed closure of cranial sutures. Patients usually present with short stature or dysmorphic features the Pediatric Endocrinology or Genetics clinics, with atypical fractures to the orthopedics clinics or hematological abnormalities to the hematology clinics. However, under-diagnosis or misdiagnosis of this condition is a major issue. Pycnodysostosis is not a life threatening condition, but craniosynostosis, frequent fractures, respiratory-sleep problems, and dental problems may cause significant morbidity. Although no specific treatment for this disorder has been described, patients should be followed for complications and treated accordingly. A specific treatment for the disorder must be established in the future to prevent complications and improve quality of life for patients in the current era of advanced molecular research.**

Keywords: Pycnodysostosis, *cathepsin K*, osteopetrosis

Pycnodysostosis is a rare autosomal recessive disorder with an estimated prevalence of 1 to 1.7 per million. The disorder is caused by a homozygous or compound heterozygous mutation in *cathepsin K* (*CTSK*), which is a lysosomal cysteine protease that is highly expressed in osteoclasts. *CTSK* is involved in the degradation of bone matrix proteins, type I and type II collagen, osteopontin, and osteonectin at a low pH (*1-7*). To date, forty-five different *CTSK* mutations have been reported, including nonsense, missense, frameshift, and splice site mutations as well as small deletions, small and big insertions (Alu sequence) (Figure 1).

The condition is also known as Maroteaux-Lamy syndrome and is characterized by a short stature, acroosteolysis of the distal phalanges, dysplasia of the clavicle, osteosclerosis with increased bone fragility, and delayed closure of sutures (*1-5*). French artist Henri de Toulouse Lautrec (1864-1901) was suggested to have this condition since he exhibited several phenotypic features of the disorder such as a short stature, parental consanguinity, facial dysmorphism, frequent bone fractures, and large fontanels (*8*). In 1994, Julia Frey claimed that Toulouse Lautrec might have had a disorder other than pycnodysostosis (*9-11*), though Maroteaux rebutted that assertion and Frey in turn defended it (*10-12*). In fact, the artist had facial features quite typical to the disorder, and confusion could be due to the evaluation of the artist's features at different ages by the two authors. In affected patients, the facial features become more prominent with age, which is most probably due to progressive acroosteolysis of the facial bones (based on the current authors' experience).

Patients usually present with short stature or dysmorphic features to the Pediatric Endocrinology

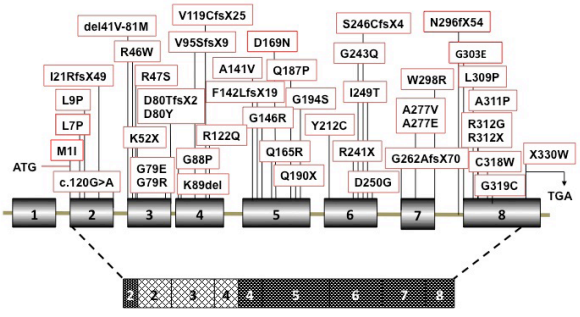

Figure 1. A diagram of the CTSK gene. The genomic structure of *CTSK* with 8 exons and a total of 45 reported mutations are shown.

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Table 1. Typical clinical features of pycnodysostosis

Skeleton
• Short stature
• Increase in bone density
• Fractures
• Stubby hands and feet with osteolysis of the distal phalanges
• Dysplastic nails
• Clavicular dysplasia, congenital pseudarthrosis of the clavicle
• Spondylolysis
Head and Neck
Face:
• Frontal and parietal bossing
• Beaked nose
• Prominent eyes with bluish sclerae
• Hypoplasia of the maxilla and mandible
Cranium:
• Open fontanels and sutures
• Craniosynostosis
• Non-pneumatized paranasal sinuses
• Arnold-Chiari malformation
Mouth and Teeth:
• Delayed eruption of permanent teeth
• Persistence of deciduous teeth, dental crowding
• Malocclusion
• Obtuse mandibular angle
• Grooved palate

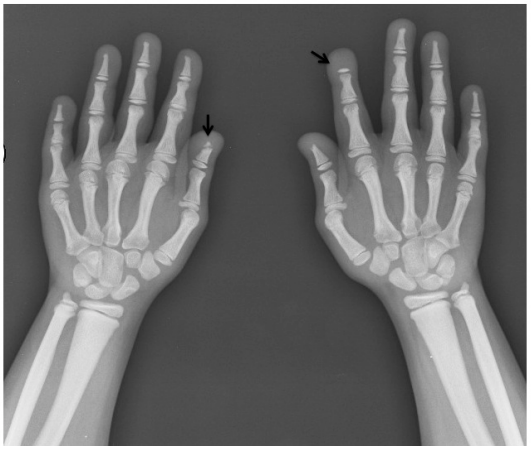

Figure 2. A typical finding of pycnodysostosis. Osteosclerosis and acroosteolysis of distal phalanges on X-rays (arrows).

or Genetics clinics and, with atypical fractures to the orthopedics clinics. A summary of the clinical features of the disorder is shown in Table 1. Pycnodysostosis is a specific form of osteopetrosis and affected patients have osteosclerosis related to decreased bone resoption. Atypical facial features are usually suggestive of the disorder, but the presence of osteosclerosis and acroosteolysis of distal phalanges provides more of a definitive diagnosis (Figure 2). In a cohort of 16 patients with clinical manifestations suggesting pycnodysostosis, molecular genetic testing resulted positive for CTSK mutation in all (*13*). At this point, recognizing the disorder's clinical manifestations is important, but recognizing its dysmorphic features is sometimes difficult. Misdiagnosis can occur, especially in the absence of acroosteolysis. Absence of acroosteolysis can be misleading, and in such instances osteopetrosis is often the diagnosis (erroneously) made. This was true in several patients studied by Panrazio *et al*. (*14*), who performed exome sequencing for patients with a pedigree suggesting autosomal recessive osteopetrosis and classical features of mild to moderate osteopetrosis, like blindness, anemia or bicytopenia, and splenomegaly. Panrazio *et al*. detected *CTSK* mutations in these patients they studied. Unlike patients with osteopetrosis, patients with pycnodysostosis rarely have hematological abnormalities, and the phenotypic features of pycnodysostosis allow the disorder to be distinguished from osteopetrosis. However, facial dysmorphism may not be readily evident, and this is especially true at young ages and in different ethnic groups. However, the presence of acroosteolysis together with osteosclerosis is a highly indicative feature (*5,13*). If a patient is misdiagnosed as having osteopetrosis, this could lead to additional misdecisions such as performing a bone marrow transplant to treat cytopenia and optic atrophy (*14*). However the optic atrophy seen in pycnodysostosis is usually a consequence of craniosynostosis, so its primary treatment is neurosurgery and not a bone marrow transplant (*13,15,16*).

Pycnodysostosis is not a life threatening condition, but frequent fractures, craniosynostosis, respiratory-sleep problems, and dental problems and their treatments may cause significant suffer to the patients (*5,13-18*). In addition, the severity of the disorder in terms of height, frequency of fractures, or additional anomalies like craniosynostosis and an Arnold-Chiari malformation can vary from patient to patient even if they have the same mutation (*5,13-16*). However, patients with a more severe genotype appear to suffer fractures at a younger age (*13*), and the youngest patient with such fractures in the literature is a 10-month-old who had two siblings that died from the disorder, suggesting that the family had a more severe phenotype and/or genotype (*15*).

Although no specific treatment for the disorder has been described, patients should be followed for complications and treated accordingly by Neurosurgery, Orthopedics and Orthodontics, Respiratory Medicine, Sleep Medicine, and Rehabilitation (*5,13-18*). Maintenance of oral hygiene and regular dental care are key to preventing oral complications. Postextraction osteomyelitis can appear due to increased bone density, and risk factors should be carefully addressed while planning tooth extraction and other surgeries (*5*).

Furthermore, short stature is a significant complaint and documented final heights of patients are below 150 cm for boys and 130-134 cm for girls. Recently, growth hormone therapy has resulted in a significant improvement in height velocity and final height in pycnodysostosis (*19,20*). Almost half of affected patients have a growth hormone deficiency but all

have low IGF-1 levels, and administration of growth hormone results in a satisfactory elevation in IGF-1 (*21,22*). Patients with a growth hormone deficiency also have pituitary hypoplasia, but no abnormalities in other pituitary hormones and pubertal development have been detected (*21*).

Pycnodysostosis is a rare clinically distinct entity with a number of different clinical signs and is usually under-diagnosed. Geneticists as well as orthopedists, hematologists, endocrinologists, and even neurosurgeons should aware of this condition. In addition, a specific treatment for the disorder must be established in the future to prevent complications and improve quality of life for patients in the current era of advanced molecular research.

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