

Pycnodysostosis—A Sparsely Diagnosed Entity and an Underrecognized Cause of Growth Hormone Responsive Reversible Short Stature: An Update



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ABSTRACT

Context: Pycnodysostosis (PYCD) is an osteopathic disorder usually present with dental or bony abnormalities. Though short stature is universal in this condition and responds to growth hormone treatment, the majority of subjects cannot reach target height because of late presentation to an endocrinologist.

Evidence acquisition: A literature review was undertaken to analyze clinical presentation and management of the disease. The rarity of the disease revealed very few case reports. The maximum number of cases were reported from India, the US, and Brazil. Most cases were concerned about their dental or osseous complications and consulted accordingly.

Evidence synthesis: Short stature, both prenatal and postnatal, is the most important but remediable complication of this disease, not adequately taken care of so far. Growth hormone deficiency has been found in some of these patients. Growth hormone treatment is effective in reaching target height whether or not its deficiency is overt.

Conclusion: All patients with facial dysmorphism, dental crowding, dense bones, recurrent fractures, and short stature should be genetically screened for PYCD. Growth hormone treatment should be considered after excluding contraindications.

Keywords: Growth hormone deficiency, Pycnodysostosis, Short stature.

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INTRODUCTION

Pycnodysostosis (PYCD) is a rare autosomal recessive disorder with a reported prevalence of 1–1.7 per million, with equal sex distribution.¹ It is due to a mutation of the lysosomal cysteine protease enzyme cathepsin K (*CTSK*), expressed adequately in osteoclasts and involved in their function. It helps in the degradation of type 1 collagen, maximally present in bones. So, a loss-of-function mutation of *CTSK* causes less osteoclast-directed bone resorption and consequent deranged bone remodeling, leading to osteosclerosis. PYCD presents with facial dysmorphism, unerupted and crowded teeth, acro-osteolysis, repeated fractures, and short stature. Parental consanguinity is common but not universal. Though it is primarily an osteopathic disorder often leading to short stature, the maximum number of cases reported are from faciomaxillary and dental specialties, and the most common presentation of this disorder is tooth crowding and the presence of multiple deciduous teeth. A proper diagnosis and consequent precautions should be taken before doing any dental surgery, as mandibular osteomyelitis is very common. Local vascularity and immunity of the affected region are affected by the

disease, which may be the cause of infection and osteomyelitis.

GENETICS

PYCD has been recognized for a long time, but it was known as osteopetrosis or other bone disorders. It was Maroteaux and Lamy who, in 1962, first conclusively described it as a separate entity. Genotype–phenotype relationship is very strong in PYCD. Those with more complete genetic aberrations manifest at a younger age with marked skeletal changes, repeated fractures, and growth retardation. Subjects with fewer mutations show normal height velocities and reach target height. Recurrent fractures are also sparse in this group. The *CTSK* gene has been located on the long arm of chromosome 1 (1q21.3, OMIM 601105). It contains 8 exons. Most mutation points are found in exons 6 and 7.² A study in a Mexican family, reported as early as 1996, detected a mutation in nucleotide 862, from C to T, of the *CTSK* coding sequence.³ Another study reported in the same year confirmed a gene mutation in the *CTSK* gene.⁴ Mutation analysis done in 1999 showed that an affected protein reduction of up to 80% in parents of affected subjects did not show any disease manifestation. Only complete absence of *CTSK* leads to

disease manifestations.⁴ In the same study, they found a nonsense mutation of A to T at DNA 154 and a missense mutation of G to A at DNA 236.⁵ In the year 2000, four cases of PYCD were analyzed; they found mutations A277V and L9P, and a single-base deletion, 531delT.⁶ In a report from Egypt of eight cases, all offspring of consanguineous marriages, homozygous missense mutations, DNA 164, A to C, and DNA 433, G to A, were found.⁷

CLINICAL PRESENTATION

The most common clinical presentation is persistent deciduous teeth and delayed teeth eruption. This persistence of deciduous teeth along with erupted permanent teeth causes supernumerary teeth and crowding. Teeth show enamel hypoplasia, caries, obliteration of pulp chambers, and malocclusion. The next common presentation is generalized increase of bone density, recurrent fractures, delayed closure of fontanelle, and short stature. The maximum reported cases are from dental and faciomaxillary surgery departments. The typical facial dysmorphism, like midface hypoplasia, retrognathia, obtuse mandibular gonial angle, frontal and sometimes occipital bossing, dolichocephaly, beaked nose, and ocular proptosis, often leads to diagnosis. Extremities show short, stocky hands and feet, dystrophic nails, and osteolysis of terminal phalanges. Clavicular dysplasia of the acromial end should be differentiated from more common cleidocranial dysplasia. A classical presentation of short stature with increased bone density is present in PYCD. All biochemical parameters of bone

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metabolism are usually normal. Thyroid and other hormones are normal. Growth hormone (GH) and IGF-1 are often low, but this finding is not universal. Others have hypothesized that when exogenous GH is administered, there is less degradation of IGF-1 at the growth plate due to *CTSK* deficiency.⁸ This may be the cause of growth stimulation of subjects with otherwise normal GH secretion. A recent case report from India has reported multiple pituitary hormone deficiencies in a case of PYCD.⁹ A report from Egypt has shown that seven out of a series of eight children reported were born short; length SDS was -3 to -1.5 . There was also postnatal growth retardation. All of them had height SDS below -3 at the third birthday. Combined genetic and hormonal factors were responsible, as they found impaired GH response on provocative tests in 50% of children. Moreover, these subjects with GH hyposecretion also had pituitary hypoplasia on MRI.¹⁰

Due to alteration of the anatomy of the palate, maxillae, and mandibles, these patients may present with obstructive sleep apnea. A study has found 37.5% of PYCD patients had sleep apnea.¹¹ They have recommended polysomnography for all patients with PYCD. Presence of a long soft palate and maxillary and mandibular deficiencies are the principal etiological factors of upper airway obstruction.¹²

A case of bilateral optic atrophy with blindness due to thickening of optic canals as a result of bone thickening has been recently reported. So, all these patients should undergo careful optic nerve examination so that early intervention could prevent blindness.¹³

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of PYCD is suggested by typical clinical features supported by radiological findings. It is confirmed by molecular genetic diagnosis of *CTSK* gene mutation. The three Ds should point to suspicion—they are dysmorphic face, dental crowding, and dense bones.

The four main differential diagnoses are osteopetrosis, cleidocranial dysostosis, idiopathic acro-osteolysis, and genetic asymmetric short stature with facial dysmorphism. The main presenting feature of osteopetrosis is multiple cranial nerve palsies over years due to strangulation at cranial foramina, along with signs of extramedullary hematopoiesis due to bone marrow dysmyelopoiesis, which often results in hepatosplenomegaly. Cleidocranial dysostosis shares many of the features of

PYCD, but the main difference is that there is no increase in bone density in the former. It usually presents with a frontal groove due to incomplete closure of the suture and open fontanelle. The clavicles are either hypoplastic at the acromial end or, in extreme cases, completely absent. Idiopathic acro-osteolysis does not show other features of PYCD. Distal phalanx osteolysis may be due to connective tissue disorder or primary Raynaud's phenomenon. But if there is midshaft osteolysis of the terminal phalanx, also called "band osteolysis," then idiopathic acro-osteolysis is the most probable diagnosis. However, a combination of osteosclerosis along with acro-osteolysis is almost diagnostic of PYCD.

MANAGEMENT

Management of this disease is primarily fivefold: (1) Management of dental and faciomaxillary aberrations; (2) Management of bone and joint fractures and deformities; (3) Management of sleep apnea; (4) Management of hematologic complications arising out of bone thickening and consequent compromise of bone marrow; (5) Management of short stature.

As we have already discussed, the most common presentation of PYCD is dental crowding and delayed eruption. Patients often consult initially for enamel hypoplasia and periodontal disease. Enamel hypoplasia leads to carious teeth and needs strict oral hygiene to prevent it. So, maintenance of dental and oral hygiene is of utmost importance. Mandibular osteomyelitis is very common, which may be spontaneous or secondary to tooth extraction. Infection with both aerobic and anaerobic organisms prevails. Antibiotics often fail to reach the site of infection due to compromised circulation to bones as a result of osteosclerosis. Midface hypoplasia is one of the important causes of dental malocclusion and consequent recurrent injury. Midface advancement surgery may help to minimize osteomyelitis. But any elective operation on these already vascularity-compromised bones may also precipitate osteomyelitis. There is a report from Istanbul of three cases that underwent successful similar operations.¹⁴

The management of fractures is according to the site affected. Utmost care should be taken to prevent osteomyelitis in these vascularity-compromised bones.

The management of upper airway obstruction depends on the site of obstruction, namely nasal, oropharyngeal, or hypopharyngeal obstruction. Long soft palate, increased tongue mass and its retroposition, and maxillary and mandibular deficiencies

produce obstruction in this region commonly. Uvulopalatopharyngoplasty and other surgical maneuvers are undertaken for these.¹⁵ Orthognathic surgery, such as maxillary and mandibular advancement, is often done.¹⁶ Due to exaggerated bone growth, there is less pneumatization of paranasal sinuses and less space inside the orbit, which may require corrective surgeries.

Hematological complications like anemia, though rare in PYCD, have been reported in some cases. Treatment is usually symptomatic.

Management of short stature is very important. Though, till date, only GH deficiency has been found, other endocrine evaluations may be done for better understanding. Growth hormone (GH) treatment for PYCD started long back in 1996, when Soliman et al. found low IGF-1 and a positive GH stimulation test in three out of four patients with PYCD. In his report from Oman of four children, all were born of consanguineous marriages. All subjects had height standard deviation (HtSDS) below -3 before starting GH treatment, and there was a significant increase in height velocity in all subjects after GH treatment.¹⁷ The same author, in another report of eight subjects, among whom four had GH hyposecretion, successfully treated short stature with GH, resulting in increased HtSDS.

Recently, there have been several studies of GH treatment of PYCD subjects. Rothenbühler et al., in a study of three patients, found a considerable increase in height velocities. They concluded that PYCD is the only form of short stature that could be totally corrected by GH therapy.⁸ In another study, they took eight children between 3 and 6 years, all of whom had height standard deviations below -3.5 , and all had delayed bone age and subnormal GH response to clonidine. They were treated with GH. There was a significant increase in height velocity as long as GH treatment was continued but significant slowing after stopping. So, from this study, it is obvious that GH treatment should be continued for a sufficient period until height velocity plateaus.¹⁸ In another single-case study, GH treatment was started at the age of 7 years when height velocity was 3.9 cm/year. GH treatment caused a rapid spurt to 9.4 cm/year.¹⁹ So, the above evidence supports that further research, including a meta-analysis, is needed on the role of GH treatment in PYCD, so that a guideline can be formulated.

CONCLUSION

PYCD is a disease with multisystem involvement. Though bone and oropharyngeal complications and their management have

been adequately addressed and advanced, growth disorder in this condition has not been studied enough. Further studies of central and peripheral causes of growth retardation in this disorder are needed for better management.

REFERENCES

1. Turan S. Current research on pycnodysostosis. *Intractable Rare Dis Res* 2014;3(3):91–93.
2. Xue Y, Cai T, Shi S, et al. Clinical and animal research findings in pycnodysostosis and gene mutations of cathepsin K from 1996 to 2011. *Orphanet J Rare Dis* 2011;6:20.
3. Johnson MR, Polymeropoulos MH, Vos HL, et al. A nonsense mutation in the cathepsin K gene observed in a family with pycnodysostosis. *Genome Res* 1996;6(11):1050–1055.
4. Gelb BD, Shi GP, Chapman HA, et al. Pycnodysostosis, a lysosomal disease caused by cathepsin K deficiency. *Science* 1996;273(5279):1236.
5. Ho N, Punturieri A, Wilkin D, et al. Mutations of CTSK result in pycnodysostosis via a reduction in cathepsin K protein. *J Bone Miner Res* 1999;14(10):1050–1055.
6. Fujita Y, Nakata K, Yasui N, et al. Novel mutations of the cathepsin K gene in patients with pycnodysostosis and their characterization. *J Clin Endocrinol Metab* 2000;85:425–431.
7. Otaify GA, Abdel-Hamid MS, Mehrez MI, et al. Genetic study of eight Egyptian patients with pycnodysostosis: identification of novel CTSK mutations and founder effect. *Osteoporos Int* 2018;29:1833–1841.
8. Rothenbühler A, Piquard C, Gueorguieva I, et al. Near normalization of adult height and body proportions by growth hormone in pycnodysostosis. *J Clin Endocrinol Metab* 2010;95:2827–2831.
9. Verma V, Singh RK. A case report of pycnodysostosis associated with multiple pituitary hormone deficiencies and response to treatment. *J Clin Res Pediatr Endocrinol* 2020;12(4):444–449.
10. Soliman AT, Ramadan MA, Sherif A, et al. Pycnodysostosis: clinical, radiologic, and endocrine evaluation and linear growth after growth hormone therapy. *Metabolism* 2001;50(8):905–911.
11. Basikizoglu N, Gokdemir Y, Turan S, et al. Sleep disordered breathing in pycnodysostosis patients. *Eur Respir J* 2014;44:P2277.
12. Muto T, Yamazaki A, Takeda S, et al. Pharyngeal narrowing as a common feature in pycnodysostosis—a cephalometric study. *Int J Oral Maxillofac Surg* 2005;34(6):680–685.
13. Schmidt GS, Schacht JP, Knee TS, et al. Pycnodysostosis (osteopetrosis acro-osteolytica). *AACE Clin Case Rep* 2020;6(5):e257–e261.
14. Capan EÇ, Turan S, Kılıçoğlu H. Clinical and cephalometric analysis of three cases with pycnodysostosis: case reports. *J Istanbul Univ Fac Dent* 2015;49(1):51–55.
15. Aghili H, Tabatabaei SMA, Goldani Moghadam M. Clinical and radiographic features of pycnodysostosis with emphasis on dentofacial problems. *Case Rep Dent* 2017;2017:4352485.
16. Hernández-Alfaro F, Arenaz Búa J, Serra Serrat M, et al. Orthognathic surgery in pycnodysostosis: a case report. *Int J Oral Maxillofac Surg* 2011;40(1):110–113.
17. Soliman AT, Rajab A, AlSalmi I, et al. Defective growth hormone secretion in children with pycnodysostosis and improved linear growth after growth hormone treatment. *Arch Dis Child* 1996;75:242–244.
18. Karamizadeh Z Md, Ilkhanipoor H Md, Bagheri F Md. Effect of growth hormone treatment on height velocity of children with pycnodysostosis. *Iran J Pediatr* 2014;24(2):161–165.
19. Yılmaz GC, Kara C, Onay H, et al. Growth hormone treatment in an adolescent with pycnodysostosis. *J Clin Res Pediatr Endocrinol* 2015;7(Suppl 2):77–92.