

Case Report

Pycnodysostosis: a distinctive brittle bone disease?

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ABSTRACT

Pycnodysostosis is a rare disorder that is inherited as an autosomal recessive trait usually diagnosed at an early age with an estimated incidence of 1.7 per 1 million births. It is a rare clinical entity, first described in 1962 by Maroteaux and Lamy. The disease has also been named Toulouse-Lautrec syndrome, after the French artist Henri de Toulouse-Lautrec, who suffered from the disease. Pycnodysostosis is a lysosomal storage disorder of the bone caused by a mutation in the gene that codes the enzyme Cathepsin K causing osteosclerosis. However, the diagnosis is sometimes late, made as a result of bone fracture, given the severe bone fragility resulting from increased bone density. Oral and maxillofacial manifestations of this disease are very common.

Keywords: Cathepsin K, Lysosomal, Osteosclerosis, Pycnodysostosis

INTRODUCTION

Pycnodysostosis (PKND) is a rare autosomal recessive skeletal abnormality acknowledged as a distinct entity by Maroteaux and Lamy in 1962. More than 150 cases have been reported from all racial groups and more than 30% of cases are the product of consanguineous parents. A review of 78 cases by Sedona and associates found a 1:1.6 male predilection, while 54 cases reviewed by Muto found a slight 1:1.3 female predominance. Patients with PKND usually have normal intelligence, sexual development and life spans.¹

The clinical manifestations of PKND commonly include increased bone density, bone fragility, and short stature. Other clinical features include skull deformities with open cranial sutures, an obtuse gonial angle of mandible, hypoplastic paranasal sinuses, dysplastic lateral clavicles, shortened terminal phalanges, proptosis, blue sclera, and frontal/occipital bossing. Oral manifestations include a flattened mandibular angle, grooved palate, anterior

crossbite, malpositioned teeth associated with an increased incidence of dental caries and periodontitis, hypoplastic maxilla and chin, delayed eruption of permanent teeth, delayed exfoliation of deciduous teeth, hypoplasia of the roots, and obliterated pulp spaces.^{1,2}

The locus for PKND maps to the human chromosome 1q21.9. The defective gene has been identified recently as that encoding cathepsin K, and PKND is now classified as a lysosomal disorder caused by defective tissue-specific expression of this enzyme.³ We report a case with PKND, presents the maxillofacial clinical features, osteomyelitis of the jaw bone, multiple fractures of long bones and discuss management issues for this type of patient.

CASE REPORT

A 35 year old male patient reported to the department with a chief complaint of dull continuous pain in the legs and right lower jaw since 1 and half year and pus

discharge from the right lower region of the jaw. On history patient gives history of frequent bone fracture on trivial injuries, unable to walk properly due to pain, he underwent extraction with right first molar which does not heal completely there was continuous dull pain with pus discharge which not healed after antibiotic therapy. Drug, medical and family history was noncontributory. Patient was conscious co-operative, well oriented to time and place; obey to the commands with abnormal gait and short stature. All vital signs and parameters were within the normal limit.



Figure 1: Diffuse swelling on right side of face with sinus opening.

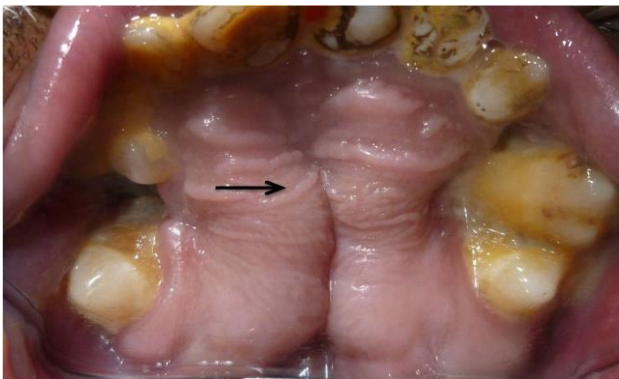


Figure 2: Characteristic oral features include deeply grooved palate and upper anterior crowding.

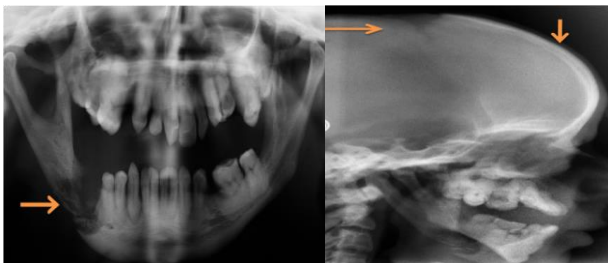


Figure 3: Panoramic radiograph showing obtuse angled mandible with mixed radiolucent and opaque lesion with sequestrum, skull X-ray showing, open anterior and posterior fontanelle, frontal bossing and non-pneumatized sinuses.

On general physical examination the patient was poorly built and nourished with short stature, short finger and

toes (Figure 4) and scoliosis (Figure 5) on examination of face there was diffuse swelling on right side of the face with external sinus opening at right lower jaw region (Figure 1). Patient has abnormal palate with deep groove (Figure 2) and Frontal bossing of the forehead (Figure 3).



Figure 4: Hands showing short stubby spoon shaped digits, X-ray showing short terminal phalangeal bones.

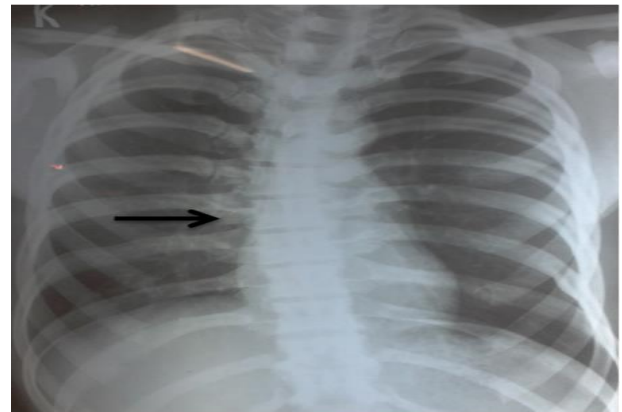


Figure 5: Chest x-ray showing right lateral scoliosis.

The base line investigations like complete blood picture, random blood sugar was done with serum alkaline phosphatase enzyme to rule out other bony disorders, culture sensitivity of pus. Radiological examination like panoramic radiograph, PA skull and long bone x-rays were performed. Panoramic radiograph revealed mixed predominantly radiolucent with radiopaque lesion on right side of jaw (Figure 3), with irregular periphery with sequestrum suggestive of osteomyelitis of right lower jaw (Figure 3). PA skull shows large cranial suture with anterior open fontanelle with frontal bossing (Figure 3). Long bone x-rays revealed multiple fractures malunited with sclerosis (Figure 6).

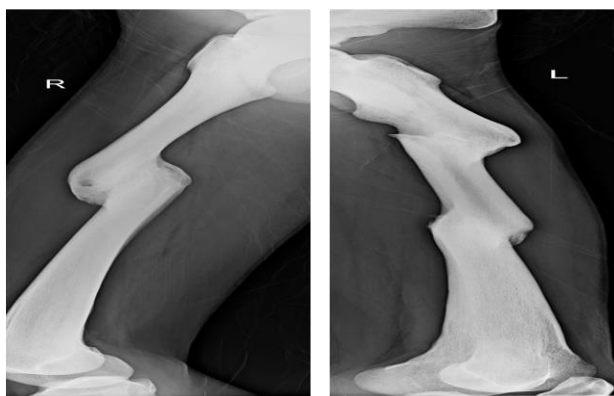


Figure 6: x-ray of right and left femur showing multiple malunited fractures with sclerotic bones.

Based on clinical and radiological feature we provisionally thought of osteomyelitis of right lower jaw and fibrous dysplasia of long bones and differential diagnosis like osteogenesis imperfecta, osteopetrosis, chronic sclerosing osteomyelitis and pycnodysostosis. Further we referred patient for the genetic analysis then genetic report showed the gene for PKND has been mapped to the same location as the gene for cathepsin K on chromosome 1q21.

Based on the clinical, radiological and the genetic test we finally diagnosed as Pycnodysostosis. Acute symptoms are addressed with hydration and broad spectrum IV antibiotics (Amikacin 500mg three times a day for 27 days). Such patients need multidisciplinary approach. An awareness and information about the disease is given to the patient and orthopedic opinion was sought for multiple fractures and referred to oral surgeon for the treatment of osteomyelitis of jaw. Later patient was referred for genetic counseling and further follow up.

DISCUSSION

Pycnodysostosis is an inherited disorder of the bone caused by a mutation in the gene that codes the enzyme cathepsin K. This enzyme is important for normal bone cells called osteoclasts, to reabsorb into the bone and build new bone.² The normal functioning of osteoclasts in individuals with pycnodysostosis is disrupted by a lack of cathepsin K, rendering individuals afflicted with this disorder to be unable to adequately reabsorb the component of bone called the organic matrix. This process is called remodeling, which is vital for normal bone maintenance. The bones in individuals afflicted with pycnodysostosis are abnormally dense and brittle as a result of this insufficient re-absorption process.^{1,2}

The features which differentiate from other bony diseases are short stature, brachycephaly, generalized diffuse osteosclerosis and sclerosis of the terminal phalanges, hypoplastic clavicles, and history of multiple fractures of long bones. The jaw and collar bone (clavicles) are also particularly prone to fractures. Craniofacial features

include a large head with fronto parietal bossing, open soft cranial sutures and fontanelles, depressed nasal bridge, a high arched grooved palate, maxillary hypoplasia, mandibular fractures, osteomyelitis, malpositioned teeth, elongated soft palate precipitating mouth breathing, and heavy snoring in addition to periapical cementoma-like lesions in the mandible. Many of these findings were present in our case which differentiates this patient from osteopetrosis and cleidocranial dysostosis.⁴

In osteopetrosis, there is no delayed closure of cranial sutures, no phalangeal, or clavicle hypoplasia. Cleidocranial dysostosis is transmitted by autosomal dominant inheritance, open fontanels and cranial sutures are also observed at an advanced age, and there is no phalangeal or clavicle hypoplasia.⁵

Osteomyelitis is the most serious complication that may arise from the oral manifestations of PKNDA. Osteomyelitis is a common occurrence in adults with PKND, but is uncommon in children. In a review of 54 reported cases in the Japanese literature by Muto and associates, nine cases of osteomyelitis were reported with the youngest case at age 20.^{5,6} In old age it is more common due to brittle bones and decreased vascularization which will continue to worsen with age. The increased susceptibility to osteomyelitis with age can be attributed to the increased endosteal bone production, which gradually eliminates the medullary spaces in the jaws and compromises vascularization and the Calcification.⁶

The diagnosis of pycnodysostosis is primarily based on clinical features and Radiographs; however a CTSK gene mutation analysis is the confirmatory test. Various novel mutations of cathepsin K gene in patients with pycnodysostosis have been reported in literature. The differential diagnosis of PKND includes osteopetrosis, acroosteolysis, mandibuloacral dysplasia, cleidocranial dysplasia and osteogenesis imperfecta. Unlike osteopetrosis, hepatosplenomegaly and anemia are rare in PKND due to the presence of active medullary hematopoiesis. The primary difference between PKND and cleidocranial dysplasia is that dense and brittle bones are found in PKND not in cleidocranial dysplasia. Fractures of the extremities in PKND are common in childhood, but the incidence appears to decrease in adulthood, probably because patients have modified their lifestyle to avoid injury.^{1,6,7}

Currently, patients diagnosed with PKND are treated symptomatically with emphasis on prevention of fractures. The recent location of the gene defect and the abnormal expression of cathepsin K will hopefully lead to new treatment possibilities for patients with PKND. Bone marrow transplant or gene therapy have been suggested as possibilities to replace the abnormal lysosomal protease expressed on osteoclasts.⁸ Until new treatment protocols are devised, education of these patients is

essential to avoid the more serious complications of PKND. Because of the morbidity associated with oro dental findings, it is essential that these patients are enrolled in a dental prevention program from an early age. Stressing the importance of exceptional oral hygiene practices and early and frequent visits to the dentist is advised to allow early intervention to alleviate many of the serious complications previously described in the literature.^{9,10}

We report here 35 old male patients with PKND, present the osteomyelitis of lower right jaw, maxillofacial clinical features and multiple fractures of long bones. A family pedigree was obtained but no other member exhibited any signs of PKND.

CONCLUSION

Pycnodysostosis is a rare genetic disease requiring proper evaluation diagnosis and multidisciplinary approaches to prevent orthopedic and oral complications. Such patients need to be educated regarding the cause, genetic counseling. Proper treatment protocols should be formulated further to manage such rare genetic diseases.

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