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CASE REPORT

Pyknodysostosis: A Challenging Diagnosis

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ABSTRACT

This case report details a 7-year-old male child with short stature, born of consanguineous parents in rural Punjab, Pakistan. Despite a normal pregnancy and early developmental milestones, concerns arose as the child aged. Clinical examination revealed frontal bossing, hypoplastic maxillae, and wide fontanelles, initially suggestive of hypothyroidism. However, further investigation, including anthropometry and skeletal surveys, revealed characteristic findings consistent with Pyknodysostosis, such as sutural diastasis and acro-osteolysis. The family was counselled regarding the condition's autosomal recessive inheritance and limited treatment options. Growth hormone therapy was proposed as a potential intervention for improved growth potential. This case highlights the importance of thorough clinical evaluation and collaboration with radiologists in diagnosing rare skeletal disorders.

Authors' Contribution:
[1,2]Conception; Literature research; manuscript design and drafting; [2,3] Critical analysis and manuscript review; [3,4] Data analysis; Manuscript Editing.

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Introduction

Toulouse-Lautrec Syndrome or Pyknodysostosis is a rare clinical entity and a diagnostic dilemma. It was first described by Marateaoux and Lamy in 1962, and was named after Henry de Toulouse-Lautrec, a French artist with a tragic life story, who, it has been hypothesised suffered from this skeletal dysplasia.[1] The disease, in some cases, so closely mimics several other skeletal abnormalities that it becomes challenging to reach a definitive clinical diagnosis.

However, in the late 90's the exact locus of genetic defect was found in the CTSK gene, resulting in a definitive diagnostic tool for this condition.[1-3] Although, due to the cost involved in genetic testing, the skeletal "Pyknotic Pentad" offers a cheap and reliable radiological assessment tool, which offers a high level of clinical suspicion for the diagnosis of Pyknodysostosis.

Case Report

We report a case of a 7-year-old male child who presented in the Paediatrics department with short stature. Born in 2012, the patient was a product of consanguineous marriage. His mother (G4P4) reports an unplanned conception, and was booked at a local hospital in the rural areas of Punjab, Pakistan. The pregnancy was well monitored, low risk and the expectant mother was well compliant with her antenatal appointments and supplementation. The mother felt quickening at 5 months, all investigations that were carried out remained normal throughout the pregnancy. The mother was immunised and her pregnancy was full term with spontaneous labour and spontaneous vertex delivery at home. The patient cried well,

immediately after delivery with a birth weight of 3 kgs, was breast fed for two years and fully immunised.

As the subject grew older, no apparent signs of developmental delay were observed for the first 2 years rather mother report an accelerated development. He started holding his neck at 2.5 months, started sitting at 6 months and walking before the age of one year. He developed stranger anxiety at 8 months, cooing and babbling by the age 9 month. However, by the age of two years, the mother started getting concerned by the physical developmental delay. The child had been to multiple healthcare setups where he was prescribed nutritional support, however no active investigations were done to the find out the cause.

The child when presented to us was fairly active, with a weight of 12 kg and a height of 95cm (below the 3rd centile) at 7 years of age. The appearance was very striking, with frontal bossing, mildly hypoplastic maxillae. initially bringing to our mind the coarse facies of hypothyroidism. However, on palpation the fontanelles were wide open and sutural diastasis was easily traceable. Thes findings along with a positive family history of a male sibling with history of repeated fractures, sensorineural hearing loss and a label of osteopetrosis, were indicative of some skeletal abnormality in this child. Detailed anthropometry yielded a near symmetrical/proportionate short stature, usually seen with endocrinopathies, making this an incredibly confusing mixed picture. A full developmental survey showed appropriate milestone achievements and interviewing the child gave us an idea of his adequate intelligence quotient with regards to the age. Detailed examination was performed checking the integrity of all major systems of the body which was completely unremarkable. Parental height was also on the upper end of average in the spectrum.

Initial Investigations at our centre included a complete blood count, thyroid profile, serum calcium, phosphorus and alkaline phosphatase and all of these investigations were within normal range. A skeletal survey was ordered which showed X-ray Skull: Sutural Diastasis with multiple Wormian bones and thickening of the Calvaria. X-ray long bones: Cortical thickening with medullary sparing and a healed fracture. X-ray spine: Spool deformity with increased density. Though the initial impression was misleading, to label the child as osteopetrosis, but several factors including the widened sutures and short stature convinced us otherwise. X-ray of the mandible showed obtuse angle, the clavicle laterally deficient and X-ray of the hand showed acro-osteolysis. Credible radiologists were included in the patient's healthcare team and after intense discussions, review of literature and additional X-rays, the patient was diagnosed as a rare case of Pyknodysostosis. The dilemma however at this point was the fact that another sibling of the patient was mislabelled. The family was counselled in detail regarding the condition, its inheritance pattern along with the unfortunate fact that 2 siblings were affected by an autosomal recessive condition. Considering the health care circumstances not a lot could be done for these patients. They were informed of the future plan of including growth hormone therapy which might result in a slightly increased growth potential.

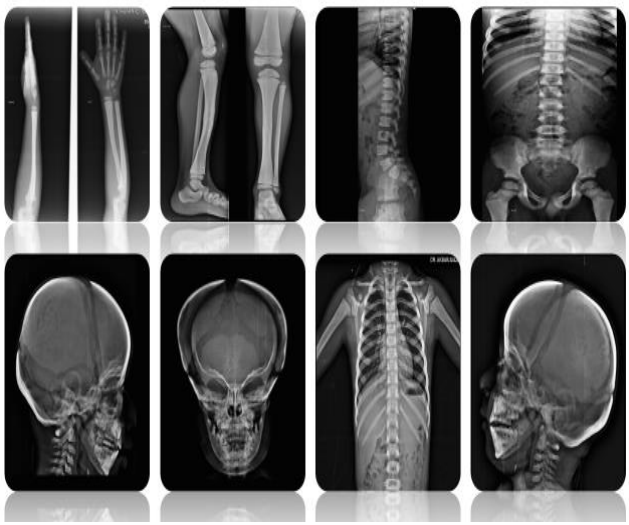

Fig. 1: X-rays showing Pyknodysostosis

Discussion

Pyknodysostosis is an autosomal recessive Osteochondrodysplasia, a lysosomal storage disorder eventually leading to osteosclerosis, as a result of a mutation in the Cathepsin K(CTSK) gene, a lysosomal cystine protease on chromosome 1q21.[7] This protease degrades Type 1 collagen which is a major constituent of the bony matrix and absence of which renders the patient vulnerable to repeated fractures due to poor bony resorption and causes failure of growth (short stature). Although, enough data has been accumulated to establish a clear diagnosis of this syndrome, but the complete spectrum of disease has not been studied due to a variety of reasons, foremost of which is the small number of cases identified. However, the patients have a normal lifespan, as of now no systemic co-morbidities have been established with this condition. As of now only 200 cases of pyknodysostosis have been reported in medical literature making its estimated prevalence to be 1 in 1.7 million.[8] The general phenotype of our patient was very characteristic. He presented with short stature, had relative prognathism, had a full array of radiological findings referred as The Pyknotic Pentad which include Osteosclerosis (Increased cortical thickness with medullary sparing, sutural diastasis/sutural non-union with Wormian bones, obtuse angle of mandible, dysplastic clavicles, and acro-osteolysis of the terminal Phalanges. Spool shaped deformity of the vertebrae along with grooving of the hard palate was also present in our patient. On further investigation no haematological pathologies were detected. Even though our patient had no other signs of systemic illness, a first degree relative who presumably had a more severe phenotype of the disease also experienced sensorineural hearing loss and more frequent fractures. Although, this cannot be said with certainty but variability in degree of expression can potentially occur in pyknodysostosis and needs to be further studied.

Pyknodysostosis needs to be kept under consideration when diagnosing a patient with conditions which can very closely mimic or have overlapping features with pyknodysostosis. Such conditions include Osteopetrosis, caused by a deficiency in the carbonic anhydrase enzyme. This disease also includes haematological derangements as its features, unlike pyknodysostosis with a potential of cure after a successful bone marrow transplant. However, if the condition is mistaken for Osteopetrosis (as in the case of sibling one of our patients) this can lead to unnecessary intervention. Other such conditions include cleidocranial dysplasia and idiopathic acro-osteolysis which should be labelled after careful clinical, radiological and haematological workup.

As of now, no specific treatment protocols have been set for pyknodysostosis. As every patient with this disease presents in the different manner treatment should be accordingly customised. A greater part of management includes thorough family counselling regarding the prognosis of the disease. According to research trial, growth hormone therapy can be given to these patients to overcome the physical growth stigmata, and it can potentially result in increased eventual height. CRISPR interference technique can be potentially employed in these patients, giving a hopeful future prospect to overcome this genetic deficiency.[9,10]

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