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Case Report

Pyle's disease in a 4-year-old boy; a rare case report

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Abstract

Pyle's disease (PD) is a rare inherited skeletal dysplasia. Approximately 35 cases have been reported worldwide. It is more frequently reported in adults. This skeletal dysplasia has distinct radiologic features, which are characterized by widening of the distal metaphysis of the femur and proximal tibia, cortical thinning, and osteoporosis. Regarding the rarity of PD and the importance of reporting its presentations, we aimed to report a 4-year-old boy focusing on its radiographic, laboratory, and genetic findings. In this case report, we present a 4-year-old boy from consanguineous parents brought to the pediatric orthopedic clinic for abnormal shape of lower extremities and difficulty walking when he was 3 years old. He was evaluated and finally diagnosed with PD using whole exome sequencing.

Keywords: Metaphyseal dysplasia, Pyle's disease, Whole exome sequencing, Children

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Introduction

Pyle's disease (PD) is a rare autosomal recessive skeletal disorder characterized by abnormal development of the long bones, particularly those of the arms and legs. The metaphysis become markedly widened, giving the bones a paddle-shaped appearance (1). Although PD is associated with bone fragility, fractures are uncommon (2).

The most consistent and prominent clinical feature is genu valgum (knock knees) (3). Other manifestations include widening of the clavicles, ribs, and bones of the hands and fingers; expansion of the ischial and pubic bones; bilateral and symmetrical enlargement of the knees, proximal humeri, and distal radii; cortical thinning at the metaphysis; delayed dental eruption; dental caries; malocclusion; a chalky appearance of bones; and reduced bone mineral density (4-6).

Mutations in the secreted frizzled-related protein 4 (*sFRP4*, OMIM 606570) gene on chromosome 7p14 have been identified as the underlying cause of PD (7, 8). The sFRP4 gene encodes a protein that acts as an inhibitor of Wnt signaling, a pathway essential for the proper development and remodeling of bones and other tissues. Disruption of this regulatory mechanism results in the bone abnormalities characteristic of PD. Fewer than 35 cases have been documented in the literature to date, and the condition is extremely rare in children (2). Given its rarity and the diagnostic value of detailed case descriptions, we report a 4-year-old boy with PD, emphasizing the radiographic, laboratory, and genetic findings.

Case Presentation

A 4-year-old boy born to consanguineous parents was evaluated by a pediatric orthopedic surgeon because of abnormal lower limb shape and difficulty walking (Figure 1). Radiographic assessment revealed osteopenia, leading to referral to a pediatric endocrinologist for further evaluation of potential metabolic bone disease or skeletal dysplasia. He was the first and only child of the family, born at 37 weeks of gestation by normal vaginal delivery with a birth weight of 2850 g. His neonatal course was notable for jaundice requiring brief hospitalization, from which he recovered without complications. Upon reassessment by the endocrinologist, a comprehensive physical, laboratory, and radiographic evaluation was performed (Figures 2–3). Physical examination revealed genu valgum and mild kyphosis in the lower limbs, while facial features and dentition were normal. Laboratory investigations showed; urea = 18.5 mg/dL, creatinine = 0.6 mg/dL, alkaline phosphatase = 402 IU/L, calcium = 9.5 mg/dL, phosphorus = 4.4 mg/dL, magnesium = 2.9 mg/dL, parathyroid hormone (PTH) = 22 pg/ml, sodium = 141 mEq/L, potassium = 3.9 mEq/L, white blood cell count = 8.9 $\times 10^9$/L, hemoglobin = 11.7 g/dL, and platelet count = 290,000/µL. Radiographic findings demonstrated an Erlenmeyer flask deformity of the metaphysis, reduced metaphyseal bone density compared to the diaphysis, absence of periosteal reaction, and preserved joint space. These findings supported the diagnosis of metaphyseal dysplasia (Pyle's disease). Subsequently, whole exome sequencing was performed using an EDTA

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Implication for health policy/practice/research/medical education

Pyle's disease is a rare inherited skeletal dysplasia with few reported cases worldwide. Raising clinician awareness and promoting radiologic and genetic diagnosis are crucial. Reporting such cases enhances understanding, supports genetic counseling in consanguineous populations, and emphasizes the importance of including rare disorders in medical education and research..

(Ethylenediaminetetraacetic acid)-anticoagulated blood sample, revealing a homozygous pathogenic variant in the SFRP4 gene (variant NM_003014.4:c.379G>T; p.Glu127), located on exon 1. According to the American College of Medical Genetics and Genomics (ACMG) criteria, this variant was classified as likely pathogenic, confirming the diagnosis of PD (OMIM 265900). Genetic counseling and parental testing for the identified variant were recommended.

Discussion

Pyle's disease is a rare inherited bone dysplasia that occurs more frequently in adults than in children. Due to its rarity, reporting new cases is valuable for enhancing clinicians' ability to recognize and manage this condition promptly; to date, approximately 35 cases have been documented worldwide (9). This disease exhibits distinctive radiologic features, most notably the widening of the distal femoral and proximal tibial metaphysis, cortical thinning, and generalized osteopenia. Similar, though often less pronounced, changes also appear in the proximal two-thirds of the humerus and distal two-thirds of the radius and ulna, while metacarpals and phalanges may show comparable alterations. Consistent with findings in previous reports, patients may also present with dental abnormalities such as caries, mandibular prognathism, and overcrowded or impacted teeth (2).

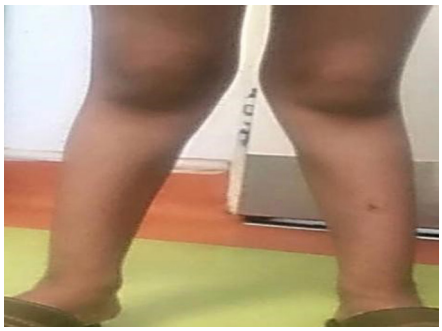

Figure 1. The appearance of the lower extremities.

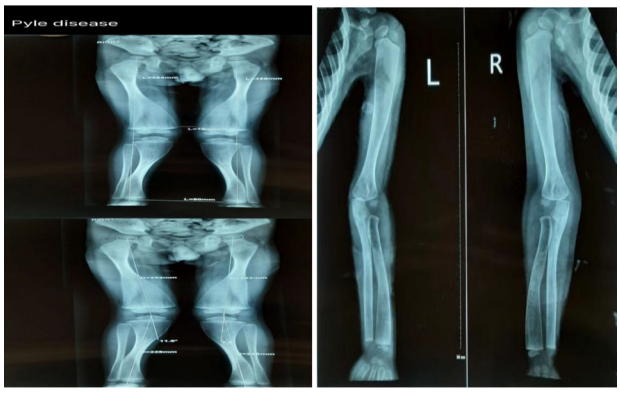

Figure 2. Radiographic results of the upper and lower extremities.

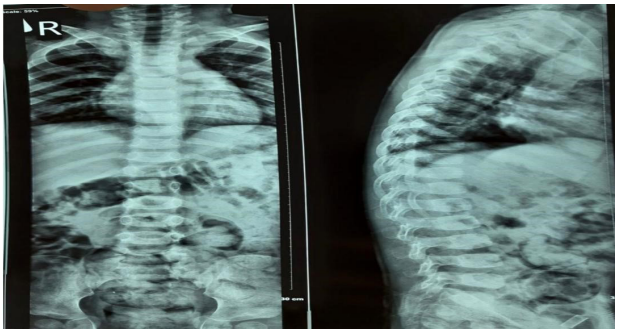

Figure 3. Deformity of the vertebral column.

Diagnosis of PD relies primarily on detailed clinical evaluation and radiologic assessment, with conventional radiography playing a crucial role in identifying its characteristic bone deformities and prompting confirmatory genetic testing of the SFRP4 gene. This gene encodes a protein that inhibits Wnt signaling, a key pathway in the development and remodeling of bones and other tissues. Proper regulation of Wnt signaling ensures normal bone turnover, involving the resorption of old bone and formation of new bone. Mutations in SFRP4 disrupt this regulation by preventing the synthesis of a functional protein, thereby leading to the skeletal abnormalities characteristic of PD. Most patients do not require medical or surgical intervention; however, orthopedic management may be indicated in cases of severe genu valgum or bone fractures (1,10).

In the present report, we described a 4-year-old boy born to consanguineous parents who presented with lower limb deformities. His diagnosis of PD was confirmed through radiologic findings, physical examination, and genetic analysis, emphasizing the integral role of imaging and clinical evaluation in early detection. Pyle's disease was first described by Edwin Pyle in 1931. Gupta et al later reported a 12-year-old patient diagnosed during bone densitometry evaluation (3), documented two sisters from consanguineous parents presenting with genu valgum, normal laboratory results, and radiographic findings of bilateral Erlenmeyer flask deformity of the femorotibial metaphysis, flaring of long bone metaphysis, and mild skull base sclerosis (4).

Although PD is often asymptomatic and generally does not necessitate treatment, orthopedic or dental interventions may be required in certain cases. Genu valgum deformity can be corrected surgically through temporary tibial asymmetric epiphysiodesis or bilateral

osteotomy, which promote bone remodeling by temporarily halting growth plate development on the inner tibial surface (3).

In conclusion, despite advancements in genetic and imaging technologies, conventional radiography remains a fundamental diagnostic tool in identifying PD. When evaluating a patient with genu valgum, the presence of Erlenmeyer flask deformity should prompt consideration of this rare disorder. These cases underscore the pivotal role of radiologists in achieving timely and accurate diagnosis, thereby facilitating appropriate genetic counseling, family education, and multidisciplinary management (4).

Conclusion

Pyle's disease is a rare autosomal recessive skeletal dysplasia caused by *SFRP4* gene mutations disrupting Wnt signaling. It presents mainly with genu valgum and metaphyseal widening, while fractures are uncommon. Diagnosis relies on radiologic, clinical, and genetic evaluations. Early recognition prevents unnecessary interventions and guides proper management. Genetic counseling and family education are essential for affected families.

Authors' contribution

Conceptualization: Nosrat Ghaemi, Sara Nikpour.
Data curation: Sepideh Bagheri, Samaneh Norouzi.
Formal analysis: Samaneh Norouzi.
Investigation: Nosrat Ghaemi, Sepideh Bagheri.
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Project administration: Sara Nikpour.
Resources: Nosrat Ghaemi.
Supervision: Nosrat Ghaemi, Sepideh Bagheri, Samaneh Norouzi.
Validation: Nosrat Ghaemi, Sepideh Bagheri.
Visualization: Samaneh Norouzi.
Writing–original draft: Sara Nikpour.
Writing–review & editing: Nosrat Ghaemi, Sepideh Bagheri, Samaneh Norouzi.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

This case report was conducted in accordance with the World Medical Association Declaration of Helsinki. The patient's guardian have provided written informed consent for publication as a case report. This study was approved by the ethics committee of Mashhad University of Medical Sciences (Ethics No. IR.MUMS.REC.1404.227). Additionally, Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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