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CASE REPORT

Juvenile Paget's disease in a 12-year-old Nigerian adolescent: a case report

Emmanuel O Adeniji [1], Elizabeth E Oyenusi [2], Oluwadamilola M Oladipo [1], Chioma B Ahumaraeze [1], Taibat A Raji [1], Magdalene A Oyewusi [1], Monisola A Ademoluti [3], Anulika N Nwanekezie [3], Abiola O Oduwole[2]

[1] Paediatric Endocrinology Training Centre for West Africa, Lagos University Teaching Hospital Idi-Araba, Nigeria.
[2]Endocrinology and Metabolism Unit, Department of Paediatrics, College of Medicine, University of Lagos/Lagos University Teaching Hospital, Nigeria.
[3]Department of Paediatrics, Lagos University Teaching Hospital Idi-Araba, Nigeria.

Correspondence: Emmanuel Oluwatosin Adeniji, Paediatric Endocrinology Training Centre for West Africa, Lagos University Teaching Hospital Idi-Araba, Nigeria Email:eoluwatosinadeniji@gmail.com, ORCID-https://orcid.org/0009-0005-0086-1139

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Summary
Paget's disease (PD) is a skeletal growth disorder characterised by highly elevated bone turnover and fast skeletal remodelling. Typically, PD is a rare disease, and it develops in the later stages of life, whereas Juvenile PD is ultra-rare. We report this 12-year-old female adolescent who presented with clinical, biochemical and radiological features that are in keeping with those of PD. Patient has been commenced on Zoledronic acid injection and outpatient follow-up appropriately. The case is being reported to show that PD, even though rare, does occur in Nigerian children, and clinicians need to be aware so that they can have a high index of suspicion when a similar presentation is encountered in clinical practice.

Keywords: Adolescents, Children, Hypercalcaemia, Hypophosphataemia, Paget's disease

Introduction
Paget's disease (PD) is a skeletal growth disorder characterised by markedly elevated bone turnover and fast skeletal remodelling. [1] It affects one or more bones, but commonly the skull, pelvis, and spine. The increased bone turnover results in bone and joint pains, pathological fractures, with elevated serum alkaline phosphatase. The development of PD is influenced by the interplay of genetic and

environmental factors, with resultant clustering in families. [2] Typically, PD develops in the later stages of life, particularly in the late 50s, and affects men more frequently than women. [2] However, Juvenile PD is ultra-rare, necessitating this report. It is inherited as an autosomal recessive disorder. Few cases of PD in children have been reported in the literature, including a case report from the Czech Republic, and another case report from India, including two cases reported in a series of 51 cases also in India. [3,4,5] To the best of the investigator's knowledge, no case had been reported in Nigerian children.

Case Description

A 12-year-old female adolescent presented to the paediatric endocrinology clinic with progressive enlargement of the head of 3 years duration. The enlargement was more prominent at the temporal sides of the skull bilaterally and in the jaws. There was an associated history of hip pain and multiple bilateral hip fractures without significant trauma around 8 years of age, just before the progressive enlargement of the head was noticed. This was confirmed at an orthopaedic hospital where she first presented. The fractures required surgical repair twice. There was no history of head trauma or history to suggest sickle cell disease; the haemoglobin genotype was reported to be AA. The child had had normal growth up till the time of onset of the symptoms. There was no hearing or visual loss or dysfunction. The neurodevelopment was essentially normal, and the child had good academic performance in school. There was no history of a similar condition in the family. Examination of the child revealed macrocephaly with a head circumference of 67cm (52-56), macrognathia, and craniofacial disproportion (as shown in Figure 1). The weight is 31kg (5th centile) and height is 125.7cm (<3rd centile, i.e short stature), with a normal body mass index of 19.6kg/m^2 (between 50th and 85th centile). The blood pressure and other vital signs were normal. Examination of the upper limbs revealed widened elbow and wrist joints, genu valgus deformity was noted on the lower limbs and rachitic rosary on the chest. Serum investigations showed hypercalcaemia of 2.94mmol/L [2.20-2.75], hypophosphataemia (0.64mmol/L [0.97-1.68]) and normal sodium, potassium, chloride and bicarbonate. Alkaline phosphatase (ALP) was markedly elevated (3106.7IU/L [0-277])



Figure 1: Picture showing macrocephaly, macrognathia, and craniofacial disproportion

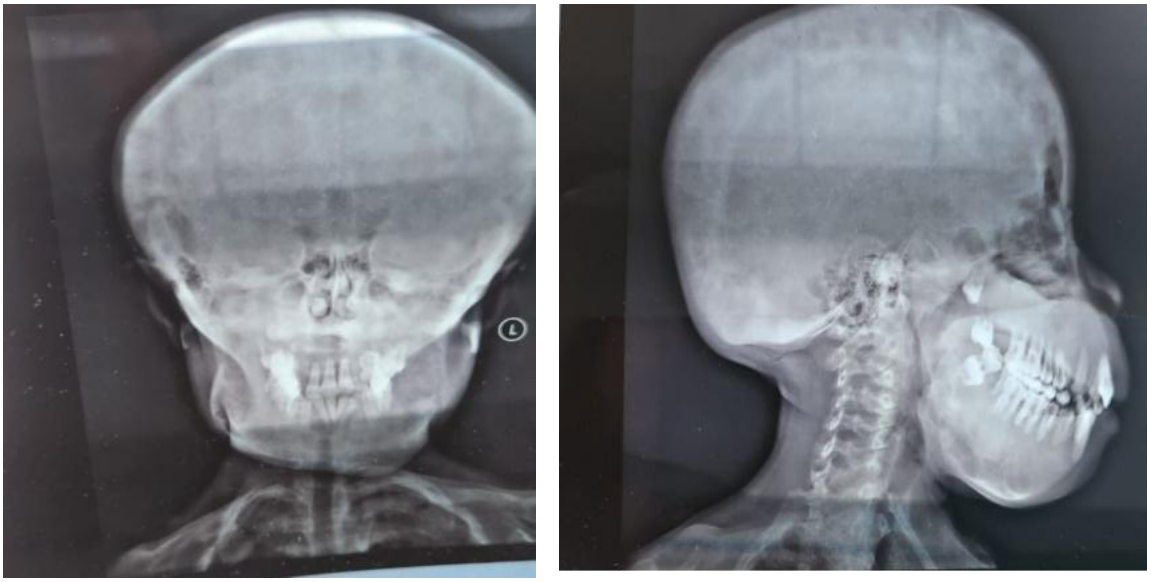


Figure 2: Skull X-Rays showing widening of the diploic space and increased size of the mandible

Skull radiographs (Figure 2) showed widening of the diploic space, increased size of the mandible, while radiographs of the hand and wrist showed resorption of distal phalanges, fusion of epiphysis to metaphysis of the phalanges and metacarpals, suggestive of hyperparathyroidism. The bone age was appropriate with the chronological age. The patient has been commenced on Zoledronic acid injection (a bisphosphonate), which is the mainstay of medical management.

Ethical consideration: Informed consent was obtained from the child's parents for the publication of this case report. They willingly gave permission for the use of clinical data and images, with an understanding of the educational and advocacy value of the case.

Discussion

Paget's disease is a complex disease that involves both genetic and environmental factors. Multiple genes have been implicated, including SQSTM1 gene, TNFRSF11A, TNFRSF11B, ZNF687 and PFN1 etc. [2] These genes play an important role in osteoclast differentiation and its function. [2,6] The involvement of genetic factors can explain the clustering that was observed in some families. Juvenile PD is usually a result of mutation of the TNFRSF11B gene, and it is inherited as an autosomal recessive disorder; hence, it tends to manifest in younger age group. [7] The TNFRSF11B gene encodes osteoprotegerin, which inhibits osteoclast activation. A mutation in the SQSTM1 gene can lead to osteoclast activation, which has been implicated in 10-15% of patients with sporadic Paget's disease and 25-40% of those with familial forms. [2,6]

Environmental factors implicated in the pathogenesis include viral infections, such as measles, which remains a significant problem in tropical regions such as Nigeria, where our patient lives. [8] Evidence to suggest

environmental factors include variability in the severity of the disease. Other factors implicated in the pathogenesis of the disease include aging, sedentary lifestyle, cigarette smoking or passive wood stove smoke, diet that is high in saturated fats and low in calcium and vitamin D. The role of environmental influences in the development of Paget's disease is not well understood, however viral messenger RNA of the paramyxovirus family e.g measles virus has been identified in osteoclasts of many patients with Paget's disease. [9] The disease can be prevented in at-risk individuals, or the progression slowed by avoiding the environmental risk factors. [10]

This metabolic bone disease is characterised by increased bone resorption by the osteoclasts that heralds the initial "lytic phase" followed by compensatory increased activity of osteoblasts that results into "sclerotic phase".[11] The enhanced osteoclast activity is due to the loss of function of osteoprotegerin, which functions to inhibit osteoclast activation. [2] This leads to enhanced osteoclastogenesis and accelerated skeletal remodelling. The increased bone resorption and compensatory increased osteoblastic activity led to pathological fractures and abnormal bone growth in our patient.

Paget's disease can be diagnosed through clinical, radiographic, and biochemical assessments, as was done in the current case. The classical PD is extremely rare in children, and diagnosis is unusual before the age of 50 years, with the majority being asymptomatic and incidentally discovered through elevated alkaline phosphatase. Paget's disease is rarer in children because exposure to environmental triggers and the development of the disease take decades to appear clinically. The index case is likely due to a genetic mutation in the TNFRSF11B gene, as mentioned above, given the age of presentation; however, genetic studies could not be performed because they are not readily available. Only few cases have been reported in children in the literature. [12,13] Common clinical manifestations of the disease, including bone pains, pathological fractures, bone deformities such as genu varum, as well as enlargement of the bones, were observed in the patient. [2] The disease usually causes severe morbidity for the patient, and when left untreated, they become wheelchair bound by 15 years of age. [7] Rickets is a close differential diagnosis of Paget's disease, but children with rickets do not have enlargement of bones or disordered bone growth as seen in Paget's disease. [2,14] The markedly elevated serum ALP in the patient suggests a lot of osteoblastic activity leading to new bone formation. [15] This finding is in keeping with the case reported by Saki et al[12] and Kumar et al. [13] In addition to the finding of elevated ALP in PD, there is increased bone resorption by osteoclasts, resulting in elevated urinary N-telopeptide levels. [15] This marker of bone resorption produced by osteoclasts was, however, not measured in the index patient as it is not readily available in our environment. The hypercalcemia and hypophosphatemia seen in our patient are contrary to the case reported by Kumar et al. [13] These could have occurred because of calcium release from bones from excessive osteoclastic resorption and also hyperparathyroidism in the index patient, but unfortunately, parathyroid hormone assay was not done due to financial constraints. Hyperparathyroidism could have occurred because of high skeletal demand for calcium for new bone formation and fluctuating levels of serum calcium. The hormone can also reduce renal phosphate reabsorption, hence causing hypophosphataemia.[16]

The increased bone resorption leads to a decrease in bone density, wedge-shaped bone resorption in the long bones, and significant osteolytic regions in the skull. Plain X-rays showed a mixed sclerotic and lytic appearance depending on the stage of the disease. These processes eventually lead to bone deformities as

seen in the index patient. The disease is associated with severe morbidity, with the majority of children becoming wheelchair bound by 15 years if untreated. Rarely, some patients can have sarcomas such as osteosarcomas, chondrosarcoma, or fibrosarcoma, although their incidence is less than 1%. [17]

Early use of bisphosphonates, like Pamidronate, alendronate, Zoledronic acid and others, prevents severe deformities, arrests progression of disease, and further fractures. [1,18] Bisphosphonates act by promoting osteoclast apoptosis, hence reducing bone resorption and bone loss. [19] These effects indirectly shift bone metabolic activity in favour of bone formation and an increase in bone mass and density. [19] Bisphosphonates administration leads to a reduction of the previously elevated alkaline phosphatase level, which is a marker of disease activity. [19] This child is currently commenced on zoledronic acid, and she is to be followed up at the endocrinology clinic. The first-degree relatives have a higher risk of developing Paget's disease; hence, screening with serum alkaline phosphatase assay every two to 3 years is recommended.

Limitation: We were unable to do a genetic mutation analysis for the patient. This would have enhanced the quality of the report, though it does not alter the management already instituted.

Conclusion

Although Paget's disease is rare in children, it does occur. It should be suspected in a child in a setting of recurrent pathologic fractures, abnormal bone growth and markedly elevated alkaline phosphatase.

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Contributions of authors: All the authors conceived the study after managing the case together. AEO and OEE did the literature review and the manuscript write up. All the authors revised the manuscript draft for sound intellectual content and approved the final version of the manuscript.

Conflicts of interest: None to declare

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