Original Article

Rickets and osteomalacia in Saudi children and adolescents attending endocrine clinic, Riyadh, Saudi Arabia

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ABSTRACT

This is a retrospective study in which we report our clinical experience during the period from January 1990 to December 2009, from a paediatric endocrine clinic at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia. The diagnosis of rickets and osteomalacia was based on clinical, biochemical and radiological data. Eighty-one (34 males and 47 females) children and adolescents with rickets or osteomalacia aged 2 to 18 years (mean; 9.5 years) were evaluated. The commonest causes were nutritional; either low Vitamin D or calcium, or both. In 58 (71.60%) patients, eight patients (9.87%) were due to chronic use of anticonvulsant medications, while five (6.17%) patients were diagnosed to have celiac disease. Non-specific symptoms, such as bone pain and fatigue were the most common presenting symptoms which may indicate that other cases were possibly missed. Lack of direct sun exposure and malnutritional practices were evident. Several genetically inherited disorders were diagnosed; including; hypophosphataemic rickets in three (3.70%), vitamin D-dependent-rickets type 2 in five (6.17%) and pseudohypo-hyperparathyroidism in one (1.23%) child. Rickets was secondary to chronic renal failure in only one patient (1.23%).

In conclusion, a diversity of disorders caused rickets or osteomalacia in our series. Paediatricians should be familiar with such different types and able to differentiate them from disorders mimicking rickets.

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rickets, such as hypophosphatasia, and metaphyseal dysplasias. An active plan should be put in place to prevent rickets and osteomalacia among young age groups.

Key words: Rickets, osteomalacia, children, Saudi Arabia, pattern, clinical presentation.
Running title: Childhood rickets in Saudi Arabia

INTRODUCTION
Rickets is the failure of mineralization of growing bones and cartilage. Initial descriptions of rickets were provided by Daniel Whistler and Francis Glisson in England as early as the 17th century. At the turn of of the 20th century, with industrialization, this disease became endemic until it was discovered that exposure to sunlight and cod liver oil could both prevent and treat rickets. This led to the search for a chemical factor which was later isolated as a fat soluble factor termed “Vitamin D”. In late 1960’s, the metabolic pathways of Vitamin D were elucidated. The hydroxylation at the 25 and 1 positions in the liver and kidney respectively, leads to calcidiol (25 hydroxycholecalciferol) and calcitriol (1,25dihydroxycholecalciferol). The latter being the most active metabolite [1-4]. Nutritional rickets is still the most common type [5-8]. Other causes of rickets include calcium and phosphorous deficiencies, inherited forms of hypophosphatemic rickets and Vitamin D metabolism defects, including receptor mutations [9-17].
In most developing regions worldwide, nutritional rickets is a prominent health problem probably because the risk factors still operate. In the Kingdom of Saudi Arabia, despite having economic affluence and adequate sunshine all year round, Vitamin D deficiency is fairly common in infants, children, adolescents, as well as pregnant and lactating mothers [18-28].

In this report, we present our clinical experience with rickets in children and adolescents aged 2-18 years from one pediatric Endocrine clinic, Riyadh, Saudi Arabia, highlighting the pattern and clinical presentation.

MATERIALS AND METHODS
Children and adolescents, aged 2-18 years, who were seen and evaluated, at King Khalid University Hospital (KKUH), Pediatric Endocrine Clinic, during the period from January 1990 to December 2009, and confirmed to have rickets were included. KKUH is the major teaching hospital of King Saud University, Riyadh, Saudi Arabia. The diagnosis was based on clinical, biochemical and radiological features as suggested:
Data were reviewed and analysed included age, sex, presenting symptoms and signs, detailed family history, clothing, housing, sun exposure, colour of the skin, dietary practice and medication intake, as well as careful physical examination. Laboratory investigations included complete blood count, renal, liver and bone profiles and serum concentrations of 25-OH-VitD (25-OH-Vit D). Test for PTH levels and 1,25dihydroxy Vitamin D (1,25 (OH)2 Vit D) and serological studies for celiac disease (anti-gliadin, anti-reticular and anti-endomyseal [ELISA immunoassay] antibodies) were carried out if indicated. Small bowel biopsies were done to confirm the diagnosis of celiac disease if indicated. The diagnosis of celiac disease was based on recommended criteria [27]. Small bowel biopsies were done to confirm the diagnosis of celiac disease if indicated. All patients were treated with oral vitamin D preparation, calcium and appropriate dietary restriction if needed. Diagnosis of inherited forms of rickets and conditions mimicking rickets were based on criteria suggested.
RESULTS
During the study period, January 1990 through to December 2009, eighty-four children and adolescents were evaluated for possible rickets or osteomalacia. Three patients were proven to have other clinical disorders other than rickets; metaphyseal dysplasia in two, and hypophosphatasia in one. Eighty-one (47 females, 34 males) children and adolescents aged 2 to 18 years with a mean of 9.5 years, were diagnosed to have rickets or osteomalacia. All were Saudis from the central region of Saudi Arabia. There were various etiologies of rickets and osteomalacia in this group (Table 1). The commonest one was nutritional which constituted 71.60% while genetic forms were approximately 11.11% of the total.

Fifty eight (71.60%) patients with nutritional rickets or osteomalacia have shown the main symptoms and signs of the diseases (Table 2). Non-specific symptoms, such as bone pains and aches were the most presenting symptoms in 39 (67.20%) patients. Short stature in 12 (20.69%), while skeletal deformities and pathological fractures were the presenting symptoms in 11 (18.97%) and 4 (6.90%) patients respectively. Muscle weakness was evident in 6 (10.34%) patients, three of them had severe weakness. Only three (5.17) patients presented with hypocalcaemia tetany, one of them was following a weight reduction trial for obesity. Bone profiles at the time of diagnosis revealed a mean serum calcium of 2.1 mmol/L, range 1.4-2.3 (normal; 2.2-2.6), phosphorus of 1.6 mmol/L, range 0.8 – 2.6 (normal; 1.4 – 2.1), and serum alkaline phosphatase activities of 1480 u/l, range 760 – 2950 (normal < 600). Serum concentrations of 25-OH-VitD were low, ranging between less than 10 to 25 nmol/L (normal: more than 50 nmol/L or 20 ng/ml). Three patients with limbs deformities, two females and one male, had hypophosphataemic rickets. A six year old boy presented initially with abnormal gait to a pediatric clinic was found to have hypocalcaemia, serum calcium of 1.47 mmol/L (normal; 2.2 – 2.6), and hyperphosphatemia, phosphorus of 2.5 mmol/L (normal; 1.4 – 2.1). The serum alkaline phosphatase activity was high at 1957 u/L (normal; less than 600). He had marked rachitic changes on X-ray of left femur with lytic and cystic
changes were evident and attributed to secondary hyperparathyroidism. A year later, he presented with fractured left femur despite being on Vitamin D and calcium therapy. He was diagnosed to have pseudo-hypo-hyperparathyroidism on molecular genetic studies. The details of this patient will be published elsewhere.

**Table 1- Etiology of rickets or osteomalacia in 81 patients.**

<table>
<thead>
<tr>
<th>Type of rickets</th>
<th>No. of patients (%)</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of males</td>
</tr>
<tr>
<td>Nutritional rickets</td>
<td>58 (71.60)</td>
<td>23</td>
</tr>
<tr>
<td>Anti-convulsant medication induced</td>
<td>8 (9.87)</td>
<td>3</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>5 (6.17)</td>
<td>0</td>
</tr>
<tr>
<td>Vitamin-D dependent rickets type 2</td>
<td>5 (6.17)</td>
<td>5</td>
</tr>
<tr>
<td>Hypophosphataemia rickets</td>
<td>3 (3.70)</td>
<td>1</td>
</tr>
<tr>
<td>Pseudo-hypo-hyperparathyroidism</td>
<td>1 (1.23)</td>
<td>1</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>1 (1.23)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 2- Clinical symptoms and signs in 58 patients with nutritional rickets or osteomalacia.**

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone aches and pain</td>
<td>39</td>
<td>67.2</td>
</tr>
<tr>
<td>Short stature</td>
<td>12</td>
<td>20.69</td>
</tr>
<tr>
<td>Skeletal deformities</td>
<td>11</td>
<td>18.97</td>
</tr>
<tr>
<td>Fractures</td>
<td>4</td>
<td>6.90</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>6</td>
<td>10.34</td>
</tr>
<tr>
<td>Tetanic spasm</td>
<td>3</td>
<td>5.17</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In this study, we have shown that in a major city of central Saudi Arabia, rickets is caused by diversity of disorders; with Vitamin D deficiency being the commonest. Nutritional rickets remains prevalent worldwide. During periods of rapid growth, where Vitamin D and other nutrients necessary for bone mineralization, rickets constitutes a major problem. Saudi Arabia, lies between latitude 24-420 North and Longitude 46-430 East. The weather is usually sunny throughout the year, and indicates that enough ultraviolet light to maintain adequate vitamin D synthesis and availability throughout the year [28, 29]. Several national studies indicated that level of 25-OH-VitD is deficient in the majority [23, 30]. Also, Bedouins living in tents had a higher level of Vitamin D than the residents of cities [18]. Avoidance of sun exposure, therefore, seems to be the reason. The importance of adequate nutrition, including Vitamin D and calcium intake in the etiopathogenesis of rickets is well established. Several studies from Africa and Asia showed rickets resulting from inadequate calcium intake in the presence of normal Vitamin D levels [9-13]. The daily calcium intake by our children and adolescents was found to be below the recommended daily allowance. This indicates lack of nutritional education, the current increase in the popularity of fast food and high consumption of soft drinks instead of milk in the study population. Therefore,
a low threshold for assessing Vitamin D sufficiency in children and adolescents is highly recommended, given also the increasing knowledge about effects of Vitamin D not only on bone mineral metabolism but also on the immune system and related disorders. A screening tool for Vitamin D deficiency rickets is serum alkaline phosphatase, when elevated should be followed by measurements of serum 25-OH-VitD, calcium, phosphorous and parathyroid hormone, along with radiological examination of the distal ends of the radius and ulna or tibia and femur depending on the age of the child. Alkaline phosphatase level is usually less than 500 IU/L in neonates and even higher in growing children, which decreases after puberty. The range varies depending on the method used for the assay. Some studies, however, indicate that not all patients with osteomalacia have high alkaline phosphatase levels, and thus, the radiograph may be more reliable test especially for detecting sub-clinical state [8, 18, 19].

Therefore, the best and accurate way to assess Vitamin D status is still to measure 25-OH-Vit D levels. In children, it has been recommended that a serum 25-OH-Vit D level of ≤ 37.5 nmol (15 ng/ml) should be considered as indicative of a deficiency and more than 50 nmol/L (20 ng/ml) as indicative of Vitamin D sufficiency, and currently severe deficiency is somewhat arbitrarily defined as a 25-OH-VitD level of ≤ 12.5 nmol/L (5 ng/ml) [3, 31-36].

Celiac disease is caused by intolerance to dietary gluten in a genetically susceptible individuals, characterized by an atrophic small intestinal mucosa on biopsy, leading to malabsorption and associated clinical abnormalities. Rickets and osteomalacia can be the initial clinical presentation of Celiac disease in children and adolescents and indicates the necessity of including it as an important cause of vitamin D deficiency [37-39].

In a community, where the rate of consanguineous marriage is high (54%), it is not unusual to see high rate of metabolic bone diseases [42, 43]. Several inherited disorders were encountered in our series. A detailed history, including family history, and a comprehensive physical examination suggest the diagnosis. Familial hypophosphatemic rickets is usually inherited as an X-linked dominant. An autosomal dominant and a recessive inheritance have been described. A phosphate-regulating gene with homology to endopeptidases on the X-chromosome (PEX gene) is mutated. The main abnormality is a defective tubular reabsorption of phosphate, leading to a permanent urinary phosphate leak. Main clinical findings include major bowing of the legs and growth failure. A defect in the renal 1-alpha-hydroxylation is transmitted as a recessive inheritance and causes the condition known as Vitamin D dependent rickets type 1. This is characterized by normal levels of 25-hydroxy-Vitamin D and low levels of 1,25dihydroxy Vitamin D. Muscle weakness and rickets are the prominent clinical findings. A normal physiological dose of 1-alpha-hydroxy-Vitamin D3 or 1,25dihydroxy Vitamin D3 is sufficient to maintain normal remission of rickets in this condition. The gene for 1-alpha-hydroxylase located on chromosome 12 has now been cloned. The type 2 Vitamin D dependent rickets resulted from a spectrum of intracellular Vitamin D receptor (VDR) defects and is characterized by the
early onset of severe rickets associated with alopecia. This condition is attributed to mutations in the (VDR) gene. Patients have normal 25-hydroxy Vitamin D levels and markedly elevated 1,25dihydroxy Vitamin D levels. Massive doses of Vitamin D analogues and calcium supplements are usually required for treatment but the response is variable. The inheritance appears to be autosomal recessive with a striking clustering of patients around the Mediterranean Sea [16, 17].

Pseudohypoparathyroidism, represent a wide spectrum of endocrine disorders, characterized by unresponsiveness to PTH. In pseudohypoparathyroidism type Ib or pseudohypoparathyroidism type I with osteitis fibrosa, the so-called pseudo-hypo-hyperthyroidism, the end organ unresponsiveness is found at the kidney, but the bone is normally responsive. These patients usually have a combination of hypocalcaemia and hyperphosphataemia with skeletal signs of hyperparathyroidism [44].

Several conditions might be confused with rickets. Hypophosphatasia, a rare metabolic bone disease that is characterized clinically by defective skeletal mineralization which manifests as rickets with variable clinical expressivity. Four types have been reported; perinatal, infantile, childhood and adult. Hypophosphatasia can be distinguished from other types of rickets by the low levels of alkaline phosphatase. It is transmitted as an autosomal recessive trait, although some mild forms seem to follow an autosomal dominant inheritance pattern. Prenatal diagnosis of perinatal hypophosphatasia has been successful. Also, a moth-eaten metaphysis rather than the classical radiological findings of rickets should raise concerns about conditions other than rickets such as metaphysialchondrodysplasia in which serum calcium, phosphorous, parathyroid hormones and Vitamin D metabolites are normal [45].

In conclusion, a diversity of causes were encountered among children and adolescents, aged 2-18 years, in our series. Although, nutritional rickets remains the commonest cause, other genetically determined disorders should not be overlooked. Special consideration should be given to patients on certain medications in particular anticonvulsants and glucocorticoids.

Malabsorption syndromes, such as celiac disease, should always be considered as an important differential diagnosis and hence indicate the need for appropriate screening. Paediatricians should be able to differentiate between different types of rickets and other medical conditions that present with skeletal deformities mimicking rickets such as hypophosphatasia and the various metaphysealdysplasias. Active plan should be put in place to prevent rickets among all age groups in the community.

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62
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