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Exploring pearls and pitfalls in the diagnosis of rickettsia among children: Mini-review and case report

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Abstract

Rickets, a condition causing softening of bones in children, is prevalent in developing regions like the Middle East, Africa, and Asia. Diagnosis of rickets can be challenging due to their non-specific symptoms, often resembling other infectious or inflammatory diseases. Nevertheless, early detection and treatment of rickets remain a global priority. Hence, gaining valuable insights into its clinical presentation, diagnostic complexities, treatment options, geographical distribution, and preventive measures is essential to ensure improved healthcare for affected children.We present a case of a 10-year-old female patient who was brought to the hospital with a history of frequent falls while playing and experiencing leg pain. The patient had poor eating habits, disliked snacking, and was not exclusively breastfed. Physical examination revealed her legs being shaped like the letter "X," with hyperlaxity and a genu valgum posture. Laboratory results indicated low levels of inorganic phosphorus and total vitamin D 25-OH. The X-ray examination showed Erlenmeyer Flask Deformity, bilateral genu valgum, bilateral distal femur, and proximal tibia metaphyseal widening deformities, and no fractures or other deformities. The patient was diagnosed with rickets and promptly treated with calcium, vit D3, multivitamin syrup, and a high protein, high-calorie diet. After one month of treatment, the patient reported reduced pain, improved balance, and fewer falls.Rickets can be prevented through effective education of parents and pregnant women about calcium and vitamin D-rich food sources and the significance of sun exposure. Pregnant women should be advised to receive a daily intake of 600 IU of vitamin D. For breastfed infants and those consuming less than 500 mL of fortified formula daily in their first year of life, oral vitamin D supplementation of 200-400 IU per day is recommended.

Keywords: Rickettsia, children, diagnosis, risk, case report

1. Introduction

The disease *rickets*, also known as rachitis, is common in developing nations, particularly in the Middle East, Africa, and Asia. Between 3 and 18 months of age is when rickets is most prevalent (1,2). Rachitis is a condition of pediatric bone softening and osteopenia with irregular calcification, resulting in a higher proportion of osteoid tissue before epiphyseal closure. The most frequent causes include poor dietary vitamin D intake and sun exposure, as well as other factors including celiac disease and hereditary disorders (3–5). It is certainly influenced by several risk factors that can increase the incidence of rickets in children (6,7).

Although clinical databases show that rickets is an uncommon disease, it is likely that clinical underdiagnosis of the condition occurs because studies meant to check healthy children for radiographic signs of rickets revealed an unexpectedly much higher frequency (8). Due to poor nutritional intake and environmental circumstances, such as avoiding sunlight, subclinical rickets is a common issue among adolescent students, particularly in girls (9). In Australia, where it is a rare disease but still affects some communities, including Indigenous Australians and immigrants, the epidemiology of rickets has also been researched (10).

Bone pain, simple fractures, early bone abnormalities, delayed fontanel closure, and softening of the skull's bones (craniotabes) are all signs and symptoms of this condition (11,12). Radiological findings, biochemical tests, the patient's medical history, and a physical examination can all be used to diagnose rickets. The most prevalent type of rickets among youngsters in Saudi Arabia is nutritional rickets, which is brought on by a vitamin D deficit (13). Osteoblasts and osteoclasts are two types of cells that have different functions specifically in the process of bone production. Calcium salts are required for osteoid, the organic part of the bone matrix, to mineralize in order for bone to mature. This process is hindered in rickets, which leads to a buildup of osteoid behind the growth plate and, over time, softening of the bone (14,15).

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Pediatricians and other medical practitioners should make an effort to ensure that kids and teens get the daily amounts of vitamin D they need based on their risk factors, cultural practices, and other variables (16,17). Starting in the first two months of life, it is advised that all newborns—including those who are exclusively breastfed—receive at least 200 IU of vitamin D daily. Additionally, it is advised that vitamin D consumption be maintained throughout infancy and adolescence because it can be difficult for some people to decide how much sun exposure is enough for them. (17-19). Although significant, ultraviolet exposure is not the sole significant factor contributing to vitamin D insufficiency. Studies indicate that due to their bigger surface area to volume ratio and stronger and better capacity to generate vitamin D, children, especially babies, may require less sun exposure than adults. Skin vitamin D synthesis depends on the exposed skin surface and duration of sun exposure. The use of topical sunscreens may hinder effective skin synthesis. SPF 30 sunscreens can cut the generation of vitamin D by 95%. Further limiting factors for solar exposure include air pollution and cloud cover. Higher elevations and sunny locations have higher UVB levels (19,20).

Lastly,hereditary factors might raise the risk of hypovitaminosis D. There have been several reports linking hypovitaminosis D to single nucleotide polymorphisms in genes linked to vitamin D. This might account for the significant inter-individual variation in vitamin D sensitivity that could affect the risk of disease. On chromosome 12q13–14, the VDR gene exhibits a number of polymorphism areas. Circulating 25(OH)D levels are also impacted by two frequent variants in the VDBP gene on chromosome 4q12-q13 (21,22).

A first period of intense therapy is followed by a second phase of maintenance therapy. For rickets, which is caused by a vitamin D shortage in the diet, there are several treatment plans available. All of them include the injection of vitamin D, either vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol), followed by follow-up checks to see if the condition has improved. Children who don't get enough calcium from their diets are given the intense phase of vitamin D treatment for two to three months combined with 500 mg of calcium supplementation through food or supplements (23). Monitoring 25-OHD levels is necessary to confirm sufficient vitamin D replacement (24). Once rickets has been controlled, bone deformities tendto regress. This improvement can often be enhanced with the use of appropriate splints. Despite adequate medical therapy and nonoperative orthopaedic measures, severe rickets deformity persists, and then operative treatment with osteotomy is indicated. Under these circumstances, vitamin D therapy should be discontinued 1 month before surgery to avoid the risk of severe hypercalcemia that would normally occur during the postoperative immobilization period (24).

When administered properly, rickets treatment is often safe and successful. Nevertheless, depending on the method of treatment and the underlying cause of the disease, there can be certain difficulties with rickets treatment. To repair skeletal deformities brought on by rickets, orthopedic care may occasionally be required. According to a study on patients with X-linked hypophosphatemic rickets, conventional orthopedic treatment can have unintended consequences include not achieving treatment objectives, leaving behind permanent sequelae, and developing new pathologies. However, rickets-related bone abnormalities may require surgery to be corrected. Although surgery is normally safe, there is a chance of complications like infections, bleeding, and problems with the anesthesia (25,26).

Rickets is a disease that may be prevented. The best strategy to avoid nutritional rickets is to inform pregnant women and parents about the value of getting enough sun exposure as well as appropriate dietary sources for calcium and vitamin D. Ideally, pregnant women should consume 600 IU of vitamin D daily together with other minerals. Additionally, infants who are breastfed and newborns who consume <500 mL of fortified formula per day in the first year of life can both get a universal 200–400 IU oral vitamin D supplement daily to help avoid rickets. High-risk populations for deficiency in vitamin D beyond infancy (children with a history of rickets and at high risk of vitamin D deficiency in their diet) should consume 600 IU of vitamin D daily, either through food or supplements (23).

2. Case Report

A 10-year-old female patient, Ms. A, residing in Jakarta, the capital city of Indonesia. Came with her parents with complaints of falling downfrequently while playing with her friends due to imbalance that had been felt since the patient was 4 - 5 years old. Other accompanying complaints included intermittent pain in the legs, especially inthe calves. When walking, the patient usually seemed to drag his leg because of the pain felt in theleft leg, especially when running. The sports teacher at the patient's school told the patient's parentsthat he could not achieve the target of running sports activities. The patient was never taken to thehospital. Since the complaints became more frequent and the patient's leg was shaped like the letter "X", the patient's parents brought him to the hospital.

The patient's mother explained that Ms. A's delivery history was at term with a birth weightof 2500 grams. A was at term with a birth weight of 2500 grams. Ms. Ms. A was known to be a poor eater since childhood, ate little rice, and did not like snacking. The patient was never exclusively breastfed and only drank formula milk (sufor). The patient was able to sit at 6 months,stand at 9 months, and walk at 11 months. Ms. A is

the fourth of four children. The first, third, and fourth child complained of the same thing and her legs were also shaped like the letter "X", exceptfor the second child. The patient's parents had no similar history. During the pregnancy of Ms. A'smother admitted that she rarely paid attention to nutrition during pregnancy, especially vitamin Dand calcium.

When measured, her height and weight were 125 cm and 20 kg. Physical examination of the patient revealed hyperlaxity and genu valgum posture. On the right leg, *true length* 71 cm and*appearance length* 73 cm were obtained, while the left leg measured *true length* 67 cm and *appearance length* 73 cm. Supporting examinations performed were laboratory examinations andradiology x-rays. Laboratory results showed that the inorganic phosphorus value level was 4.4 mg/dL and total vitamin D 25-OH was 18.5 ng/mL. The results of X-ray examination of the bilateral *long leg* region and bilateral genu as shown in Figure 1 and 2, showed that there was a picture of *Erlenmeyer Flask Deformity,* bilateral genu valgum, no significant *leg length discrepancy*, bilateral distal femur and proximal tibia metaphyseal widening deformities, and no fractures or deformities of bilateral genu bones.

Fig. 1. Physical examination results on the patient's feet. Description (1) front view inspection, (2) back view inspection, (3) measurement on the right lower limb with application, (4) measurement on the left lower limb with the application (Source: personal documentation)

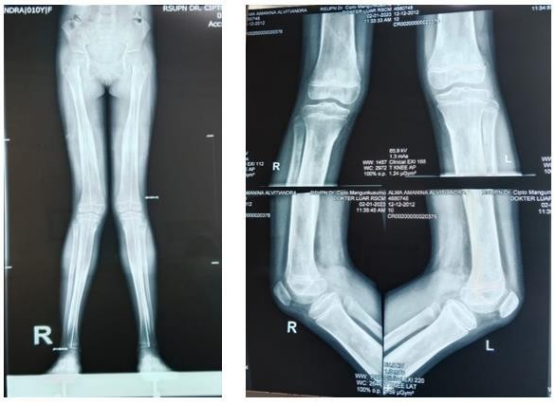

Fig.2. X-ray examination results of the patient (Source: personal documentation)

Finally, patient was given treatment of supplement tablet 1x1 tablet/day which consists of 500 mg calcium hydrogen phosphate and cholecalciferol 133 IU, Multivitamin syrup which consists of multivitamin and mineral supplements, accompanied by high calorie and high protein diets. After one month of treatment, patient developed a huge improvement in terms of reduced leg pain as well as reduced imbalance and fall frequency. Furthermore, there is also improvement in terms of laboratory findings, such as increased vitamin D and calcium level, which are 26.6 ng/mL and 9.9 mg/dL, respectively.

3. Discussion

Rickets may be divided into two primary groups. These groups consists of phosphopenic and calcipenic.(27,28) (Fig. 3.)

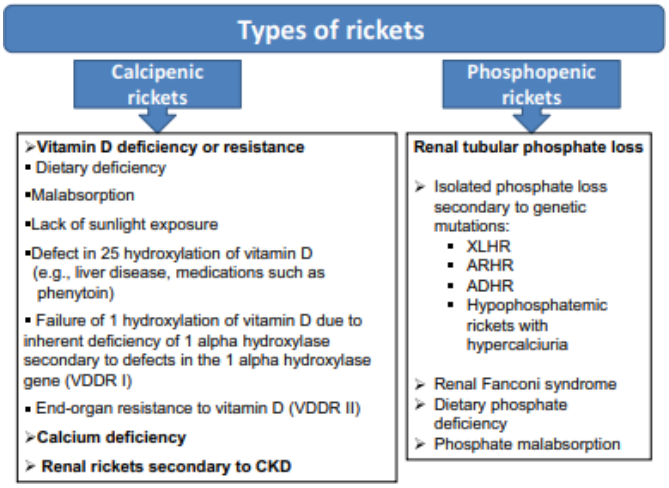

Fig. 3. Type of *rickets* (Source: Chanchlani R et al., 2020) (27).

Risk factors for rickets are described in Table 1(29). During pregnancy, the patient's mother explained that she tended to eat anything without *paying* attention to the nutrients in each food, especially vitamin D. This was also a factor of the patient being a poor eater since childhood. An increasing amount of research demonstrates that maternal hypovitaminosis D affects mother and child health. Fetal vitamin D stores throughout pregnancy are solely reliant on maternal vitamin D status (30,31). Infants only receive a maximum of roughly 40 IU of vitamin D per 750 ml of breast milk, whether or not vitamin D levels are adequate in the mother (27).

Although our patient received sufforus as a kid, she was never exclusively breastfed. According to several studies, vitamin D is abundantly consumed by formula-fed newborns since the milk has been fortified with minerals. Therefore, deficiency of vitamin D is rare in newborns who are fed formula milk (29,32). However, since the patient was not very fondof eating or snacking as a child, it is possible to make the patient's condition vitamin D deficient.

Other factors include lack of sun exposure due to the use of clothes that cover the whole body or inadequate lighting at home. It can be seen that the patient also wears a hijab when goingout. Even though Saudi Arabia has enough of sunshine and ultraviolet radiation, 100% of healthy young women there are vitamin D deficient (33-35). All of the individuals in a research with 465 female participants had low levels of vitamin D (25-hydroxyvitamin 75 nmol/l), with an average level of 18.34 8.2 nmol/l. This contradiction may result from Saudi Arabian Muslim women being expected to cover themselves completely in accordance with local customs, preventing sun exposure (35)

Clinical manifestations in pediatric patients with rickets may present with tetany or seizures due to hypocalcemia. Parents may notice that there is failure to thrive, lethargy, and muscle flaccidity. Early skeletal changes are skull deformities (craniotabes) and thickening of the knees, ankles and wrists from overgrowth plates. Enlargement of the costochondral junction ('rickety rosary') and lateral curve of the chest (Harrison's sulcus) may also occur. Limb deformities such as coxa vara and bowing. The femur and tibia bones may develop after weight bearing, while overall growth may be retarded (24).

Biochemical testing and radiographic pictures are the following steps to confirm the diagnosis if rickets is clinically suspected. Serum *alkaline phosphatase* (ALP), which is often elevated due to rickets being a condition of aberrant mineralization and enhanced osteoblastic activity, is the most crucial laboratory marker for diagnosing rickets. In rickets, phosphate shortage causes ALP activity. ALP levels are often found between 400 and 800 IU/L in cases of phosphopenic rickets, whereas values up to or exceeding 2000 IU/L are frequently seen in cases of calciphenic rickets.

Another laboratory indicator that aids in the diagnosis of rickets is the amount of serum 25-hydroxyvitamin D, particularly in cases of deficiency in nutritional vitamin D. 1,25-Dihydroxyvitamin D, which is the active form of the vitamin, has a short half-life of 5 to 10 hours. The primary circulating form of vitamin D, serum 25-hydroxyvitamin D levels, are frequently used to determine vitamin D status. Serum 25-hydroxyvitamin D levels in children with nutritional rickets brought on by vitamin D insufficiency are typically less than 10 ng/mL. Deficiency in vitamin D is defined as 25-hydroxyvitamin D levels of less than 30 ng/mL, inadequate levels of 30 to 50 ng/mL, and adequate levels of >50 ng/mL (according to the global consensus recommendations on the prevention and treatment of nutritional rickets) (23).

Serum ALP levels are elevated in most types of rickets, but in one hereditary type of hypophosphatasia rickets it is normal. However, differentiation between different types of rickets necessitates the use of a number of standard diagnostic methods. For example, elevated blood creatinine and serum inorganic phosphorus levels indicate a renal lesion, whereas abnormal blood creatinine and decreased serum inorganic phosphorus levels (hypophosphatetnia), in the absence of vitamin D deficiency, indicate a renal tubular defect (31).

The patient's condition showed clinical manifestations of *calcipenic rickets*. Supporting laboratory results were inorganic phosphorus values within normal limits (4.4 mg/dL), while total vitamin D 25-OH levels were less than normal,at 18.5 ng/mL (normal 30-100 ng/mL). X-rays revealed *Erlenmeyer flask deformity*, genu valgum, and bilateral distal femur and proximal tibia metaphyseal widening deformities.

Typical radiographic examination of changes at the ends of growing long bones, which show widened radiolucent zones at the epiphyseal plate (resulting in uncalcified preosseous cartilage) and also by the general rough appearance of trabeculations resulting from mineralizationdefects of all bony areas. Rachis modifications also include trabecular metaphysis development, *cupping*, *fraying*, and *splaying*. A *rachitic rosary* and enlargement of the costo-costal junction are visible on the chest X-ray. In more severe phases, angular abnormalities and pathological fractures of the bones in the upper and lower limbs may be seen (23).

Rickets inhibits the mineralization of osteoid, the organic component of the bone matrix, resulting in softness in the bone over time. There are two main types of rickets, which are phosphopenic and calcipenic. The patient's clinical manifestations were consistent with calcipenic rickets. Supporting laboratory results showed inorganic phosphorus values within normal limits, while total vitamin D 25-OH levels were below normal. X-rays revealed Erlenmeyer flask deformity, genu valgum, and bilateral distal femur and proximal tibia metaphyseal widening deformities

The study implies that rickets continue to be a prevalent condition in developing regions. The diagnosis of rickets can be challenging due to its non-specific symptoms. Early detection and treatment of rickets are crucial to improve healthcare for affected children. Overall, the study emphasizes the importance of raising awareness about rickets, improving diagnostic capabilities, and implementing preventive measures to combat this condition effectively, particularly in regions with a high prevalence of rickets.

Rickets is confirmed as the cause by a combination of risk factors in the patient, positive clinical signs, significant laboratory results (high ALP, hypocalcemia, or hypophosphatemia), and indicative radiographic features. Even if the serum calcium and phosphate levels are normal, the diagnosis may still be made. Similar to this, early clinical indications are not identified. The distal ends of the upper and lower extremities' quickly expanding bones, as well as pictures of the ribs, should all be visible on radiologic imaging. Although nowadays people are educated about the importance of sun exposure and vitamin D for bones, in fact rickets can still occur in people living in urban areas.

Conflict of interest
The authors declared no conflict of interest.

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Authors' contributions
Concept: B.S., H.M., Design: B.S., H.M., Data Collection or Processing: B.S., H.M., D.F.Z., P.K., Analysis or Interpretation: B.S., H.M., P.K., Literature Search: B.S., H.M., D.F.Z., Writing: B.S., H.M., P.K.

Ethical Statement

Ethics committee permission is not required for this study.

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