Current Practice

Approach to a child presenting with rickets

Navoda Atapattu[1]

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Introduction

Rickets is a disease of growing bones due to defective mineralization at growth plates in growing children. Defective mineralization of bone matrix is referred to as osteomalacia and is seen in children with rickets. Adequate calcium and phosphate levels are required for bone mineralization and vitamin D is critical for calcium homeostasis. Prevalence of nutritional rickets is rising in the developing as well as the developed countries due to changing lifestyles and globalization[1,2].

Aetiological classification of rickets

1. *Calcipenic rickets* can result from inadequate vitamin D, defective utilization of vitamin D or inadequate calcium and includes:
    - Nutritional vitamin D deficiency
    - Calcium deficiency
    - Vitamin D deficiency secondary to:
        - Malabsorption
        - Antiepileptic drug therapy
        - Chronic renal failure
        - Liver failure
    - Distal renal tubular acidosis
    - 25 hydroxylase deficiency in liver (rare)
    - Vitamin D resistant rickets
2. *Phosphopenic rickets* is not common, but occurs in special situations:
    - Low phosphorous intake
    - Prematurity/ Total parenteral nutrition
    - Renal phosphate wasting
    - Proximal renal tubular acidosis
    - Fibrous dysplasia
    - Oncogenic hypophosphataemic rickets
    - Hereditary hypophosphataemic rickets:
        - X -linked dominant (XLH)
        - Autosomal dominant
        - Autosomal recessive
        - Hereditary hypophosphataemia with hypercalciuria (HHRH)

[1]*Senior Registrar in Paediatric Endocrinology, University Paediatric Unit, Lady Ridgeway Hospital, Colombo*

Clinical presentation

Clinical history plays an important role in delineating the cause of rickets. Consanguinity, family history of rickets, dietary patterns, history suggestive of chronic renal or liver disease and malabsorption are important factors to consider. The symptoms of rickets are due to soft bones, weakness of muscles and hypocalcaemia. Clinical features vary among different age groups.

During infancy, irritability, sweating, seizures, jitteriness, cardiomyopathy, delayed milestones, delayed dentition, craniotabes, delayed closure of anterior fontanelle and bossing of the skull can be seen. *In the older child*, waddling gait, Harrison sulcus, rachitic rosary, genu valgum, genu varum (intercondylar distance more than 5cm) or windswept deformity are known to occur. *In adolescence*, seizures and bone pain are the major features one would encounter. Short stature may be a feature in hypophosphataemic rickets.

Investigations

1. *Biochemical investigations*
    - Calcium, alkaline phosphatase, phosphate
    - Liver functions
    - Renal functions
    - Serum parathyroid hormone (PTH)
    - Plasma 25 hydroxyvitamin D (25OHD)
    - Plasma $1,25(OH)_2D3$
    - Urine calcium, phosphate, creatinine
    - Tubular reabsorption of phosphate (TRP)
    - Tubular maximum for phosphate reabsorption ($TmPO_4/GFR$)
2. *Radiological investigation*
    - X- rays of wrist and knee

Alkaline phosphatase levels are usually high in calcipenic rickets whereas they are marginally elevated in phosphopenic rickets. PTH is the most important biochemical investigation which is elevated in calcipenic rickets but usually normal in phosphopenic rickets. However phosphopenic rickets due to mutations of Klotho (a cofactor) will result in hypophosphataemic rickets with

hyperparathyroidism. PTH measurements are not freely available in resource poor settings. It is however, possible to manage these patients without performing PTH levels unless we are dealing with hypophosphataemic rickets.

Calcipenic rickets

Vitamin D deficiency rickets

The serum level of 25OHD is currently considered to be the most appropriate marker of the Vitamin D status of an individual. 25OHD level of less than 50nmol/l is considered as deficiency according to Institute of Medicine Guidelines[3]. There are three stages of vitamin D deficiency:

1. Hypocalcaemia due to poor intestinal absorption and reduced bone resorption.
2. Normal calcium and low phosphate state due to secondary hyperparathyroidism
3. Severe bone disease with recurrence of hypocalcaemia.

Measurement of 25OHD is not available in the state sector in Sri Lanka. Based on the clinical history and in the absence of a chronic underlying condition, a trial of treatment with vitamin D and calcium is considered rational in resource limited settings[4]. After 1-2 months of treatment a repeat x-ray should be done to look for the line of healing. Serum alkaline phosphatase also should show a downward trend at the end of one month. If biochemical or radiological evidence of response is present, nutritional rickets could be diagnosed and treatment continued for 2-3 months. Thereafter, maintenance with daily intake of vitamin D 400units is recommended at least for 6 months. Treatment of vitamin D deficiency should be with either ergocalciferol (D2) or cholecalciferol (D3). The dose regime is as follows[5]:

< 6 months of age	- 3,000 units daily
6 months -12 years	- 6,000 units daily
>12 years	- 10,000 units daily

If malabsorption, liver disease or compliance is an issue, a single oral or intramuscular dose of vitamin D 150-300,000 units can be given every 3 months. Other suggested treatment regimens are as follows:

- Infants and toddlers - 10,000U/kg (maximum 150, 000U)[6]
- Adolescents - 10,000U/kg (maximum 600,000U)[7]

It is important that adequate calcium intake is given to these children with nutritional rickets as they are at risk of dietary calcium insufficiency[4]. In the absence of radiological healing after 2-3 months of treatment with vitamin D and calcium it will be necessary to check 25OHD and plasma $1,25(OH)_2D_3$ (Figure 1) to diagnose the underlying condition.

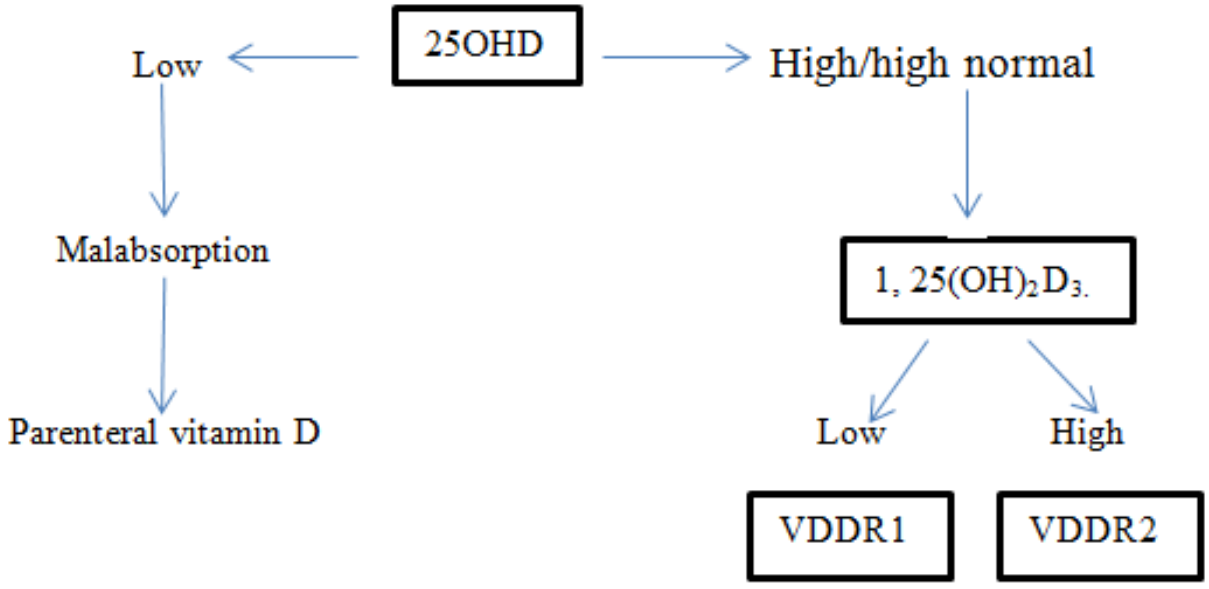

Figure 1: ***Investigation of rickets not responding to vitamin D therapy***

Vitamin D resistant rickets

Vitamin D resistant rickets type 1 (VDDR1) is due to 1 alpha hydroxylase deficiency. They usually present during the toddler age group. Biochemical features are similar to vitamin D deficiency rickets: hypocalcaemia, hypophosphataemia, raised PTH and high alkaline phosphatase levels. VDDR1 is treated with alfacalcidol or calcitriol 30-70ng/kg. Initially it may require supra-physiological doses till healing of rickets. Alfacalcidol has a long half-life and could be given as a daily dose but may need a larger dose as it is less potent. Calcitriol is more potent but needs to be given in two divided doses.

Vitamin D resistant rickets type 2 (VDDR 2) is due to a mutation in the vitamin D receptor. It typically presents during infancy or toddler age groups. Mild cases may present during adolescence[8]. It is a rare condition and 50% of affected patients can have alopecia. Presence of alopecia does not determine the severity of the disease. Supra-physiological doses of calcitriol or alfacalcidol are useful in the treatment. It has been reported that phosphate treatment was useful in the treatment of VDDR2[9]. Intravenous calcium is the treatment of choice until healing occurs with attention to serum phosphate and magnesium levels. Subsequently high dose of calcium and calcitriol will be useful in the management. These patients need to be monitored for development of hypercalciuria and nephrocalcinosis. In the presence of hypercalciuria a thiazide diuretic needs to be started at a dose of 0.5-2mg/kg day.

Renal tubular acidosis

Both proximal and distal renal tubular acidosis can give rise to rickets. Normal anion gap, hypokalaemia and hyperchloraemia are biochemical hallmarks of renal tubular acidosis. Polyuria and nephrocalcinosis may be seen in distal renal tubular acidosis. Hypophosphataemia and other features of Fanconi syndrome may be associated with proximal renal tubular acidosis. Absence of increased PTH levels will differentiate proximal renal tubular acidosis from other causes of rickets which are associated with phosphaturia due to secondary hyperparathyroidism. Treatment includes alkali therapy. If there is phosphaturia, phosphate supplements will be needed for the healing of rickets.

Calcium deficiency rickets

Clinical and radiological features are similar to vitamin D deficiency rickets except craniotabes and hypotonia. These patients may present beyond 18 months of age. Treatment is calcium supplementation and improvement in dietary calcium intake. Generally 1 g of calcium daily is recommended for 6 months. Calcium carbonate is the cheapest with highest amount of elemental calcium.

Anticonvulsant induced rickets

All drugs used in seizure control predispose to vitamin D deficiency. Underlying mechanism is the activation of cytochrome P450 enzymes which also metabolises vitamin D. It has been recently recommended that children on anticonvulsants for more than 3 months should be provided supplements of vitamin D in a dosage of three times that used for normal children[10,11].

Hypophosphataemic rickets

It must be emphasized that low phosphorus levels do not necessarily mean hypophosphataemic rickets. All causes of calcipenic rickets result in secondary hyperparathyroidism and phosphaturia. The most useful biochemical marker is the PTH which is normal or minimally raised in hypophosphataemic rickets.

Abnormalities in the sodium-phosphate cotransporter in the epithelial brush border of the proximal renal tubule result in hypophosphataemic rickets. Phosphaturia results in defective mineralization of the growth plate in the presence of normal calcium, vitamin D and PTH levels.

- ***X- linked hypophosphataemic rickets (XLH)***

Inactivating mutation of PHEX gene results in XLH. Increased expression of fibroblast growth factor 23 (FGF23) results in inhibition of phosphate reabsorption and impaired production of 1 alpha hydroxylase. Affected patients usually present with bowing of legs with characteristic anterior bowing of tibia. Defective dentine can result in dental pulp abscess formation. Biochemical investigations reveal reduced plasma phosphate, increased alkaline phosphatase and low renal tubular reabsorption of phosphate (TRP %). TRP <85% is regarded as abnormal. To correct the nonlinear relationships of TRP, Tubular maximum for phosphate reabsorption (TmPO4/GFR) is derived from the normogram or calculated for the newborns and toddlers to improve the accuracy[12].

Treatment is with phosphate supplementation at a dose of 70-100mg/kg/day in 4-6 divided doses. Alfacalcidol at a dose of 25-50ng/kg once daily is given to prevent secondary hyperparathyroidism. During follow up it is necessary to look for evidence of hypercalciuria, nephrocalcinosis and secondary hyperparathyroidism. If hyperparathyroidism is

detected it is necessary to adjust the dose of alfacalcidol. Orthopaedic follow up will also needed to correct deformities. Treatment of hypophosphataemic rickets does not improve the growth optimally and there is no place for growth hormone according to recent Cochrane review[13].

- ***Autosomal dominant hypophosphataemic rickets (ADHR).***

Lower limb deformities, tooth abscesses and fractures are commonly seen. Both sexes are equally affected and some women can present in second to fourth decade of life. The clinical cause is similar to mild form of XLH. Treatment is similar to XLH.

- ***Hereditary hypophosphataemic rickets with hypercalciuria (HHRH)***

Mutation in sodium-phosphate co-transporter gene SLC34A3 results in this condition. They have hypercalciuria in addition to hypophosphataemia. In the absence of readily available genetic tests it is important to delineate the type of hypophosphataemic rickets. However it is cheaper to look for hypercalciuria before commencing treatment for patients with hypophosphataemic rickets. Treatment includes high dose phosphate at 1-2.5g/d in 5 divided doses.

- ***X linked recessive hypophosphataemic rickets(Dent disease)***

Boys present with features similar to XLH but associated proteinuria, hypercalciuria and nephrocalcinosis will differentiate from other subtypes. They can progress to renal failure. Treatment is only with phosphate supplement.

- ***Autosomal recessive hypophosphataemic rickets***.

Biochemical and clinical features are similar to XLH and ADHR and treatment is similar to XLH.

Tumour induced osteomalacia (TIO)

TIO is an acquired cause of FGF23 excess mainly seen in adults. They present with fractures, bone pain or muscle weakness. Mostly mixed connective tissue tumours give rise to this condition. Removal of tumour results in biochemical and radiological improvement.

Fibrous dysplasia

Fibrous dysplasia is caused by somatic activating mutations in the alpha subunit of the stimulatory G-protein. Non mineralizing bone lesions secrete FGF23 leading to hypophosphataemic rickets or osteomalacia. Phosphate levels need to be corrected with phosphate solutions.

Conditions associated with radiological features of rickets

Metaphyseal chondrodysplasia, Schmid, Jansen, Schwachman skeletal dysplasias and Blount disease will have similar radiological features but not the typical biochemistry. It is necessary to evaluate a child presenting with clinical and radiological features of rickets carefully before commencing on treatment.

Orthopaedic treatment

Orthopaedic treatment should only be considered after complete biochemical and radiological healing of rickets which may take 18-24 months. Mild to moderate deformities normalize by remodelling over years. If deformities interfere with mobilization surgical correction may need to be considered.

Conclusion

Rickets is a seemingly easy diagnosis in paediatric practice. However to manage a patient with rickets a careful clinical and biochemical evaluation is needed to decide on the most appropriate treatment. Once treatment is started it is difficult to re-evaluate.

Key points

- Vitamin D deficiency is common.
- Calcium deficiency can co-exist with vitamin D deficiency
- Treat vitamin D deficiency with ergocalciferol or cholecalciferol NOT calcitriol or 1 alfa calcidol.
- Do serial PTH when hypophosphataemic rickets patients are on treatment to titrate 1 alfa calcidol dose.
- In hypophosphataemic rickets, in addition to phosphate buffer treatment add 1 alfa calcidol if there is no hypercalciuria.
- Look for evidence of hypercalciuria (patients with VDDR and hypophosphataemic rickets) and treat appropriately.
- Take the second void urine sample in the morning for calcium creatinine ratio.
- Do biochemical investigations at least after 4 hours of fasting, preferably 8 hours.

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