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Nutritional rickets - A hospital-based study from Southern Kerala

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ABSTRACT

Objective: The aim of this study is to find the characteristics of nutritional rickets and the proportion of cases diagnosed prospectively. **Methods:** Details of 54 cases of nutritional rickets in the age group of 1 month-12 years diagnosed during 2013-2015 in a tertiary care teaching hospital in Kerala were collected. The criteria taken for diagnosis were clinical features, biochemical parameters such as calcium, phosphorous, alkaline phosphatase (ALP), radiological features, and response to vitamin D treatment. Vitamin D level and serum parathyroid hormone levels were collected whenever it is available. The data were then analyzed statistically. **Results:** Among the 54 cases analyzed, 61.11% were male. A maximum number of cases were identified in the age group of 1-2 years (44.44%). Nearly 88.89% of patients were born term. About 83.3% of patients were intermediate or dark skinned. The most common clinical feature identified was bowlegs. Radiological features were identified in 70.4% of cases. The most common biochemical abnormality noted was elevated serum ALP (83.33%). Hypocalcemic seizures were a predominant manifestation in <6 months' age group. Rickets was detected prospectively in 26 patients (48.15%) during evaluation for other illnesses. The mean ALP level was found to be significantly lower in patients with clinical or radiological features of rickets compared to those without clinical or radiological evidence. **Conclusions:** Rickets is very common in the age group of 1-2 years and among exclusively breastfed term babies. The significant number of cases of nutritional rickets was detected prospectively during evaluation for other illnesses. ALP level may be routinely checked in the vulnerable high-risk age group for identification of early rickets as it is significantly elevated even before clinical and radiological changes appear.

Key words: *Alkaline phosphatase, Children, Nutritional rickets, South India, Vitamin D deficiency*

Rickets is a disease of growing bone that is caused by unmineralized matrix at the growth plates and occurs in children only before fusion of the epiphysis. It is principally caused by vitamin D deficiency [1]. Nutritional rickets is distinct from other types of rickets in that it can be easily corrected if detected early. It most commonly occurs in infancy because of a combination of poor intake and inadequate cutaneous synthesis. In infants living in sun-rich countries, avoidance of sunlight because of concerns about cancer, cultural practices and decreased cutaneous synthesis because of increased skin pigmentation are the major causes. Low vitamin D content of breast milk is another cause. Decreased maternal vitamin D can also contribute to reduced vitamin D in the breast milk and reduced transplacental delivery of vitamin D [1].

Vitamin D deficiency is on the increase in countries in the equatorial region including all states of India in spite of good sunshine [2-10]. However, data of nutritional rickets among children are scarce, especially from South India. Hence, we undertook the study in a tertiary care teaching hospital in South India. Early diagnosis of nutritional rickets is often difficult. Furthermore, there are no standard criteria for diagnosis. It is a standard practice to look for evidence of comorbid conditions such as rickets in all pediatric patients when they come to us for other illnesses. However, we may miss cases of rickets until florid clinical features develop. This can happen, especially in busy institutions unless we are aware of the same and have high index of suspicion. In this context, data of rickets cases detected prospectively gain importance. This study is the first study which identifies the presence of nutritional rickets detected prospectively when children seek medical care for other illnesses.

MATERIALS AND METHODS

This descriptive study was conducted in a tertiary care teaching hospital in Southern Kerala. Permission was obtained from the Ethical Committee before conducting the study. Nutritional rickets diagnosed in children between the age group of 1 month and 12 years during 2013-2015 was included in the study. The criteria taken for diagnosis were clinical features, biochemical parameters such as calcium, phosphorous, alkaline phosphatase (ALP), radiological features, and response to vitamin D treatment. Vitamin D level and serum parathyroid hormone (sPTH) levels were collected, whenever available.

The details were collected by interviewing the caretaker, clinical examination, collecting laboratory findings, and radiological features and following up the cases after giving adequate treatment. The radiological features noted were osteopenia, cupping, fraying, and splaying at the metaphyseal end of radius, ulna, and fibula. Response to treatment was assessed by normalization of ALP or resolution of radiological features after appropriate treatment with vitamin D and calcium supplementation. Dose of vitamin D used was 3 lakhs in <1 year of age and 3-6 lakhs in more than 1 year age group. Weekly dose was administered in most of the cases. Vitamin D level was classified as deficiency (<20 ng/ml) and insufficiency (21-29 ng/ml) [11].

Each case was individually analyzed and diagnosis was confirmed as nutritional rickets before including in the study. The cause of rickets was identified to be nutritional based on the multiple parameters including a history of decreased vitamin D intake, decreased sunlight exposure, low vitamin D level, increased sPTH levels associated with decreased serum calcium or serum phosphorous levels, and elevated ALP levels. In cases where follow-up was not possible, diagnosis of nutritional rickets was made based on all the other criteria previously mentioned such as decreased vitamin D levels, increased PTH level in the setting of decreased vitamin D intake, and decreased cutaneous exposure to sunlight.

Renal rickets and hypophosphatemic rickets were excluded from the study. Abnormal serum creatinine value along with elevated serum phosphorous levels excluded renal rickets. Hypophosphatemic rickets was identified by the absence of response to vitamin D treatment, absence of elevation of sPTH level, and demonstration of elevated fractional excretion of urinary phosphorous.

These details were entered in a pro forma and taken for analysis. Statistical analysis of the data was performed with Microsoft excel and SPSS 18 software. Chi-square analysis was performed to test for differences in proportions of categorical variables between two or more groups. In 2 × 2 tables, Fisher's exact test (two-tailed) replaced Chi-square test if the assumptions underlying Chi-square violated. That is, in case where the sample size is small and the expected frequency is <5 in any of the cells. Pearson's correlation coefficient was used to evaluate the strength of association between two variables. $p<0.05$ was considered as the cutoff value for significance.

RESULTS

Among the 54 cases analyzed, 33 were male (61.11%) and 21 were female (38.89%). Male-to-female ratio was 1.57:1. Mean age was 1.99±2.06 years (range 65 days-11 years). The maximum number of cases was in the age group of 1-2 years (44.44%) as shown in Table 1. In the study population, 88.89% of the patients were born term and 10.9% had history of prematurity. Of the 54 cases, 45 (83.3%) were intermediate or dark skinned and 9 (16.67%) were fair skinned.

Clinical features of rickets were present in 43 (79.62%) cases. The most common clinical feature identified was bowlegs (57.4%) as shown in Table 2. Developmental delay was present in 16 patients (29.63%). All these patients had predominant gross motor delay. Radiological features were identified in 38 patients (70.4%). The most common biochemical abnormality identified was elevated ALP (83.33%) as shown in Table 3. Among 43 patients whose vitamin D level was checked, 36 (83.72%) had vitamin D deficiency and 7 had vitamin D insufficiency (16.28%).

Six children presented with hypocalcemic seizures, of which 4 were <3 months of age and 1 was 7 months and the other was 2.75 years old. Out of 6 infants aged <6 months, 4 had hypocalcemia. Mean calcium level in <6 months of age was 7.01±1.80 mg/dl and in >6 months age group was 9.46±1.09 mg/dl ($p=0.02$). Thus, a significantly low level of calcium is noted in infants <6 months of age. Three out of four babies aged <3 months had maternal vitamin D deficiency. One, 4-month-old, baby who was diagnosed to have lamellar ichthyosis was admitted for bronchiolitis when he was found to have elevated ALP and hypocalcemia. On further evaluation, he was detected to have radiological features of rickets and hypovitaminosis. In this case, the primary skin condition has led to decreased cutaneous synthesis of vitamin D.

Mean vitamin D level in children <6 months of age was significantly lower than in >6 months age group (7.74±7.65 vs. 13.38±6.48) ($p=0.08$). The difference in level of phosphorous, ALP, and PTH was not found to be statistically significant. Of the 43 children with clinical rickets, 34 (79.07%) had elevated ALP level (Table 4). Appropriate response to vitamin D was

Table 1: Age distribution

Age	n (%)
≤3 months	4 (7.40)
3-6 months	2 (3.70)
>6 months-1 year	9 (16.67)
1-2 years	24 (44.44)
2-5 years	12 (22.22)
>5 years	3 (5.56)

Table 2: Clinical features

Clinical feature	n (%)
Bowlegs	31 (57.4)
Knock-knees	6 (11.11)
Wrist widening	20 (37.04)
Abnormal AF	3 (5.55)
Frontal bossing	19 (35.19)
Rachitic rosary	8 (14.8)

Table 3: Biochemical parameters

Biochemical parameters	Present (%)	Done
Hypocalcemia	9 (16.67)	54
Hypophosphatemia	7 (12.96)	54
Increased sALP	45 (83.33)	54
Hypovitaminosis D (<20)	36 (83.72)	43
Vitamin D 20-30	7 (16.28)	43
Increased PTH	17 (80.95)	21

sALP: Serum alkaline phosphatase, PTH: Parathyroid hormone

obtained in 32 out of 54 patients. Follow-up was not possible in 22 patients. However, in these 22 patients, diagnosis was made taking into consideration all other features of nutritional rickets by individually analyzing each case. Two sets of twins and two sets of siblings with rickets were among the study population. Non-nutritional rickets was excluded in all of these cases by doing appropriate investigations including PTH, vitamin D level, and urinary fractional excretion of phosphorous wherever indicated.

Rickets was prospectively detected in 26 patients (48.15%) when these children got admitted for other unrelated conditions such as febrile seizures, respiratory infection, and urinary tract infection. Diagnostic clue was the clinical features in 8 cases and increased ALP level in 16 cases. Nutritional rickets was identified during routine screening in 2 patients when they came for evaluation of failure to thrive. When we got the clue for rickets, further evaluation was done and diagnosis was confirmed. The patients were grouped into prospectively detected cases and otherwise. The mean age of cases in these two groups (2.11±1.86 vs. 1.85±2.28 years) did not show any significant difference (p=0.651). Similarly, serum calcium, phosphorous, vitamin D, and PTH levels did not show a significant difference in these two groups. However, mean ALP level of the first group (1147.16) was significantly higher than the second group (596.46) (p=0.003).

ALP level was compared in patients with radiological changes of rickets and without radiological changes. The mean ALP levels in patients with radiological rickets (746.75±614.74) were significantly higher in patients without radiological changes (1189.71±866.91) (p=0.043). Participants were also grouped into children with clinical features of rickets (n=43) and without clinical features. Only serum ALP levels showed a significant difference (p=0.01) between two groups as shown in Table 5.

DISCUSSION

Vitamin D deficiency is highly prevalent worldwide [2-10]. The prevalence of vitamin D deficiency is 50-90% in the Indian subcontinent [2,12]. Clinical rickets cases are also increasingly being reported [13,14]. Vitamin D deficiency is the most common cause of rickets globally [1]. Dietary calcium deficiency also plays a pivotal role [15]. In this study, a high proportion of cases of rickets was recognized while evaluating for other unrelated conditions which highlights the importance of high index of suspicion for rickets in children, especially among the high risk. Similar studies are not available in literature which detects the presence of prospectively detected rickets.

The tool which helped most for the same was serum ALP level. In our hospital, it is a standard practice to do renal and liver function tests in all admitted sick patients which helped to detect ALP level elevation and prospectively find evidence of rickets. All other cases were diagnosed to have rickets when they came for evaluation to rule out rickets in view of florid clinical features of rickets. Where there is isolated ALP level elevation without clinical or radiological features, diagnosis was confirmed by serum calcium, phosphorous, vitamin D level estimation, response to treatment with vitamin D, elevated PTH level, and after excluding all other causes of elevated ALP level including liver disease.

In the present study, a male predilection was noted (61.11%). Similar male predilection was noted in other studies from Australia [16] and the US [13]. In our study, the maximum number of cases was in the age group of 1-2 years (44.44%). In the literature review, 22 case studies had age range from 4 to 54 months at the time of diagnosis while in 17 studies, the maximum age range was <30 months and in 15 studies, age ranged from 10.5 to 25 months [13]. In a Canadian study, the mean age at diagnosis was 1.4 years [17].

In most of the previous studies, babies born term are mostly affected. In a study of 398 children from Australia, only 9 were born preterm [16]. In a review, among the 12 studies that reported length of gestation for all cases, all except 2 cases were term babies. In our study also, 88.89% of the patients were term whereas only 10.9% were born preterm. The probable reason may be because of the practice of vitamin D and calcium supplementation given to preterm babies. Furthermore, preterm babies get formula feeds in addition to breast milk. Breast milk contains low vitamin D [1], and most of the term babies in South India receive exclusive breastfeeding without regular vitamin D supplementation.

Similar to other studies, the majority (83.33%) of our study individuals was intermediate or dark skinned. In a Canadian study [17], 89% of cases were intermediate or dark skinned. The high incidence is due to the fact that melanin in the skin decreases

Table 4: Clinical rickets and ALP level

Clinical signs	Normal ALP	Elevated ALP	Total
Rickets with clinical signs	9	34	43
Without clinical signs	0	11	11
Total	9	45	

ALP: Alkaline phosphatase

Table 5: Relation between clinical rickets and biochemical parameters

Biochemical parameters	With clinical features (n=43)	SD	Without clinical features (n=11)	SD	p value
Serum calcium	9.37	1.11	8.48	2.12	0.059
Serum phosphorous	4.80	1.45	5.80	2.06	0.067
sALP	738.16	624.64	1344.09	833.04	0.010
Vitamin D	12.35 (n=33)	5.91	13.94 (n=10)	9.38	0.523
PTH (n=14)	273.08 (n=14)	350.90	152.43 (n=3)	69.91	0.571

sALP: Serum alkaline phosphatase, PTH: Parathyroid hormone, SD: Standard deviation

the amount of vitamin D3 synthesized from the sunlight [15]. Therefore, children with dark skin need to spend more time exposed to sunlight to synthesize the same amount of vitamin D3 as fair-skinned people [13]. In a previous study, it was found that an adult with dark skin should spend 6 times more time than an adult with fair skin [18].

Regarding clinical presentation, it was found that 4 out of 6 babies in the <6 months age group had hypocalcemic seizures and all the 4 were <3 months. Of these, 3 babies were term exclusively breastfed without any nutritional supplementation. In 3 out of 4 babies with hypocalcemic seizures, maternal vitamin D deficiency was documented although they did not show any clinical manifestations. In the literature, it was found that hypocalcemic seizures were more frequent among infants than among older children [17]. In this Canadian study, 80% of the children with hypocalcemic seizures were younger than 1 year. In another study from Turkey, it was reported that nutritional rickets and vitamin D deficiency rickets can develop very early in infancy and are usually characterized by severe hypocalcemic symptoms [19]. Symptomatic hypocalcemia in young infants due to vitamin D deficiency has been reported in two studies from the UK also [20,21]. A case series of 13 exclusively breastfed infants presenting with hypocalcemic seizures with proven vitamin D deficiency has been reported from India [22,23].

In the present study, radiological features were identified in 70.4% of patients, which were similar to an Australian study showing these changes in 71% of cases [16]. In the study from the US, 159 out of 166 (95.78%) cases had radiological features [12]. In the study from Canada [17], radiological evidence was present in 93% (87/94) of the patients. The comparatively less number in our study may be because of inclusion of rickets diagnosed prospectively while evaluating for other medical conditions. Majority of the patients in the prospectively detected group were detected by the elevated ALP levels (61.6%). The mean ALP levels in children with radiological features were significantly lower than in children without radiological features. The classical radiological features of rickets include generalized osteopenia, widening of the growth plates, and cupping of metaphyseal regions of long bones [24]. Although other studies had reported that vitamin D deficiency can occur in infants and children without radiological evidence because of the increased metabolic demands due to rapid growth resulting in hypocalcemia before any radiological change could occur [20].

Regarding biochemical parameters, the most common abnormality identified was elevated ALP levels (83.33%). Furthermore, the mean ALP level was found to be lower in patients with clinical features or radiological features of rickets. From this, it can be interpreted that ALP level can be used as a screening tool to identify early rickets before the development of florid clinical and radiological features. Once these features develop, the level falls which may be due to decreased bone growth. In the present study, 61.6% of the patients in the prospectively identified group were detected with the help of elevated ALP levels. Therefore, ALP levels may be routinely checked in the vulnerable high-risk age group for identification of early rickets.

In a Nigerian study, higher prevalence of a history of bone deformities and clinical rickets among family members and first-degree relatives of children with active rickets has been noted [25]. Although it is possible that similar environmental and socioeconomic factors among family members might be responsible for the disease, this finding does raise the possibility that genetic factors might also play a role. In our study, we could identify two sets of twins and two sets of siblings with nutritional rickets.

We should be in the lookout for babies with clinical features of rickets when they come to us for other illnesses both as outpatients and inpatients and during routine checkups and immunization visits so that many can be identified before florid changes and bone deformities develop. The limitation of our study was that we have not collected data regarding diet, vitamin D supplementation, body mass index, sunlight exposure, and residence of all the patients. Vitamin D and PTH levels were not available for all the cases. However, we mainly intended to report the presence of prospectively identified rickets.

CONCLUSION

Rickets is very common in the age group of 1-2 years and among exclusively breastfed term babies, and rate of prospective detection of nutritional rickets is increasing. ALP levels may be routinely checked in the vulnerable high-risk age group for identification of early rickets as it is significantly elevated even before clinical and radiological changes appear.

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