Decline in Age of Nutritional Rickets, Need for Routine Vitamin D Supplementation in Young Infants

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Abstract

Objective: To determine the age at the diagnosis of rickets in children in a tertiary care hospital of Karachi and to assess the association of age at the diagnosis of rickets with serum levels of vitamin D.
Methods: This cross-sectional descriptive study was carried out from January 2016 to July 2017 on 240 patients >1 month to 36 months of age, both genders, admitted in the paediatric ward, Civil Hospital, Karachi for various reasons. Children having clinical signs suggestive of rickets were confirmed to have the disease by radiological evidence, raised serum alkaline phosphatase and reduced serum vitamin D levels. Children with rickets secondary to chronic diarrhoea, non-nutritional aetiologies and those taking anticonvulsants, corticosteroids, or vitamin D supplements were excluded from the study. Data was analysed using SPSS 16 for frequencies of age at the time of diagnosis of rickets and for classification of vitamin D levels into severely deficient, deficient, insufficient and normal. Association of the age at the diagnosis of rickets was tested with serum levels of vitamin D by applying chi-square test of independence. Statistical significance was considered at p-value <0.05.
Results: Mean age was 6.2 ± 5.9 months. A total of 130 (54.2%) subjects were ≤6 months of age, including 84 (35%) ≤3 months. Serum Vitamin D levels were done in 210 (87.5%) cases. Total of 168 (80%) cases were either deficient [141 (67.1%)] or severely deficient [27 (12.9%)] in vitamin D while 42 (20%) had insufficient levels. There was significant association of age at diagnosis of rickets with serum vitamin D levels. Rickets was an incidental diagnosis in most patients.
Conclusion: Nutritional rickets was most common in cases ≤ 6 months age with a sizable number ≤3 months. Vitamin D deficiency was the cause in all patients. Significant association was established between serum vitamin D levels and age at diagnosis of rickets. Most of the subjects remained undetected until they were investigated on basis of clinical suspicion.

Keywords: Rickets, vitamin D, nutritional deficiency, metabolic bone disease, children, infants
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Introduction

Rickets is defined as defective mineralisation of growing bone before the closure of the epiphysis potentially leading to fractures and deformity[1]. It is included among the top-ranking diseases affecting paediatric population in several developing countries[2], and the commonest reason of bone disease in children all over the world[3]. Causes of rickets are multifaceted, including nutritional rickets (NR), impaired metabolism of vitamin D, phosphorous deficiency, distal renal tubular acidosis, chronic kidney diseases, chronic liver diseases and skin diseases[1,2].

Although it is now well-established that the causes of NR range from isolated vitamin D deficiency (VDD) to isolated calcium deficiency, the most common underlying pathology responsible for the disease globally is recognized as vitamin D deficiency[1,2]. NR has persisted as a public health is-

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sue with VDD or insufficiency affecting almost one billion people all over the world[4]. Among developing countries it is included among the five commonest diseases of childhood, while the developed countries have witnessed a resurgence of the disease too[5]. It is prevalent in all the continents including America, Europe, Middle East, Asia and Africa with greatest burden of NR reported in Middle East, Asia and Africa[1,6,7]. The prevalence of nutritional rickets in different populations depends on their environmental condition, skin colour, and socioeconomic status and has been reported between >10% in Africa to 42% in Northern China[2,4]. High prevalence of vitamin D deficiency has been reported from China, India and Pakistan in spite of the availability of plentiful sunlight which is the main source of vitamin D to humans[4].

The importance of vitamin D deficiency lies on the major impact it has on the health of a child through adolescence to adulthood. The effect goes beyond those on the skeletal development and increased risk of fracture to contributing to the pool of potentially serious and chronic diseases with consequent complications such as diabetes mellitus, cancer, multiple sclerosis, asthma, seizures, cardiomyopathy, hypertension, cardiac illnesses in adulthood and even death[1,7,8].

Although a prevalence of about 15-18% is reported from Southeast Asia[5], we were not able to find the prevalence or incidence of rickets in our paediatric community except for a couple of old reports, in spite of extensive search, showing the frequency of rickets as 2.25% among admitted paediatric patients[9], while deficiency of vitamin D was shown in 55% of healthy infants[4]. Similar experience regarding the scarcity of local data on statistics of rickets was shared by Haider et al. too[5]. We were unable to find the peak age of diagnosis of rickets in our country, though the literature reports it between 6 and 18 months[10].

Lately, it is being observed in our clinical practice, that an increasing number of cases of rickets is being diagnosed at an age much earlier than 6-18 months, as previously taught in textbooks. Knowledge of the exact age at time of diagnosis of rickets is required to decide the appropriate age for routine supplementation of vitamin D to infants, an exercise which is being practiced in many countries in the wake of increasing incidence of VDD all over the world[6]. Therefore we decided to determine the age at diagnosis of rickets in children in a tertiary care hospital of Karachi and to assess the association of that age with serum levels of vitamin D. If we prove the occurrence of rickets in younger infants, we would recommend the routine supplementation of vitamin D before that age. This will go a long way to prevent the serious consequences of vitamin D deficiency later in life. We will also recommend the search for identification of the factors responsible for shifting of nutritional rickets to earlier age on urgent basis so that steps can be taken to do away with those factors, thus preventing the consequent morbidities throughout life.

Subjects and Methods

This cross-sectional descriptive study was carried out over a period of one and half years from January 2016 to July 2017 on all patients age 1 month to 36 months, of both genders, who were admitted in the Department of Paediatrics, Civil Hospital, Karachi for various reasons. A sample of 240 patients was calculated by the formula

$$n = \frac{Z^2 * (p) * (1-p)}{c^2}$$

from OpenEpi Version 3, using a frequency of 50% and confidence level of 97% for a population of more than 1,000,000.

Patients who were admitted in ward for various reasons and fulfilled the inclusion criteria were examined with consent of their parents for concomitant clinical signs suggestive of rickets, including widening of wrist, frontal bossing, parietal bossing, wide open anterior fontanelle (more than age-specific centile chart), bowing of legs and genu valgum (or knock knees defined as a distance of more than 5 cm between the ankles when knees are approximated).

Table 1. Age distribution of patients having rickets

Age in months	Number n= 240	%
≤3	84	35
>3- 6	46	19.2
>6- 12	58	24.2
>12- 24	44	18.3
>24	8	3.3

Table 2. Classification of levels of vitamin D according to age

Age of the patient (<5)	Vitamin D levels (ng/mL) Severe deficiency (5-14)	Deficiency (15-20)	Insufficiency	Total
≤ 3 months	18	38	11	67
>3 to 6 months	5	28	11	44
>6 to 12 months	1	42	11	54
>12 to 24 months	3	29	8	40
>24 months	0	4	1	5
Total	27	141	42	210

Those with one or more clinical sign(s) suggestive of rickets were investigated for confirmation of the diagnosis using either X-ray of the wrist for radiological evidence of rickets reviewed by an expert radiologist of the same hospital, or with biochemical tests including elevated serum alkaline phosphatase and reduced levels of serum vitamin D [25(OH)D]. Serum alkaline phosphatase level of >391 IU was considered as elevated for children 24-36 months of age and >460 IU for age 1 month to 24 months. Sera for quantifying vitamin D levels were collected whenever the test was available in the laboratory of Civil Hospital, Karachi. Vitamin D deficiency was defined as serum 25(OH)D <20 ng/mL (50 mmol/L). Radiographic evidence of rickets included a 'radiolucent' line between the epiphysis and metaphysis, expansion of the metaphysis, irregularity of the metaphyseal margin, a brush-like appearance/fraying, cupping, splaying and general osteopenia. Blood sampling was performed on subjects with permission of parents by skilled samplers via venepuncture done routinely to collect samples as part of standard management.

Children with a nutritional deficiency secondary to another disease associated with history of chronic diarrhoea (malabsorption syndromes, coeliac disease, cystic fibrosis) were excluded from study on the basis of history or medical records. Rickets secondary to other non-nutritional aetiologies (i.e. inherited bone disease, chronic kidney disease, hepatobiliary disorders or skeletal diseases) were also excluded from the study on the basis of history, physical examination and relevant investigations including serum creatinine, liver function tests and X-ray of bones,as were those who were taking anticonvulsants, corticosteroids, or preparations containing vitamin D.

Data including the age of the cases, their gender and the results of biochemical tests were entered on a predesigned proforma. Data was then analysed by IBM SPSS version 16 for the age at the time of diagnosis of rickets and biochemical results which were described in frequencies/percentages. It was further analysed to classify the levels of vitamin D into severely deficient (<5 ng/mL), deficient (5 to 14 ng/mL), insufficient (15 to 20 ng/mL) and normal (>20 to 50 ng/mL) in accordance with the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society[11]. Association of the age at diagnosis of rickets was then tested with serum levels of vitamin D by applying chi-square test of independence. Statistical significance was considered at p-value <0.05.

This study was approved by the ethical review committee of the institute (DUHS Karachi).

Results

The results of our study showed an equal distribution of gender with males and females contributing 120 (50%) each to a sample of 240 subjects. The mean age in our study was found to be 6.2 ± 5.9 months. The median age of presentation was 6 months. A total of 130 (54.2%) cases were 6 months of age including 84 (35%) who were 3 months (Table 1). Serum vitamin D levels could be done in 210 (87.5%) cases out of a total 240 because of the non-availability of the test in the hospital laboratory intermittently for brief periods of time. All of those 210 subjects showed some degree of deficit of vitamin D levels. The mean serum level of vitamin D was 10.06 ± 4.55 ng/mL, with a minimum level of 2 ng/mL and maximum of 21 ng/mL).

Analysis for classification of severity of vitamin D deficit revealed that a total of 168 (80%) cases

were either deficient [141(67.1%)] or severely deficient [27 (12.9%)] in vitamin D while 42 (20%) had insufficient levels (Table 2). Most [141 (67.1%)] of the subjects fell in the category of deficiency with serum levels of vitamin D ranging from 5-14 ng/mL.

Although most of the patients in all ages belonged to the 'deficient group', further analysis of the cases with severe deficiency for age revealed that its frequency was highest in the youngest age group of 1-3 months as compared to the older children, (Table 2). This association between age at diagnosis of rickets and serum vitamin D levels was demonstrated as significant (p-value 0.009) by the application of chi-square test of independence.

Interestingly, almost all of the patients who were diagnosed with rickets were admitted for other unrelated illnesses and rickets was incidentally diagnosed on physical examination. Most common reason for admission was pneumonia, [48 (20%)], while there were only 17 (7%) who presented with hypocalcaemic fits as the sole presentation of vitamin D deficiency (Fig. 1).

Discussion

Widespread distribution, increasing incidence in several developed countries and persistence of NR as the most common form of growing bone disease, despite the efforts of health care providers to reduce its incidence, has been well-reported in literature[4,11,12]. It is not only affecting an increasing number of population but is also affecting children at an age earlier than 6 months, as known previously[10,13].

Review of several studies from the United States reported rickets under the age of six months with ages ranging from 3-54 months. The average age in their data was 20.2 ± 8.2 months with most patients falling in the age range of 1-2 years[6,14,15]. This is much higher than the mean age of 6.2 ± 5.9 months in our study where most [84 (54.2%)] of the subjects were 6 months age, including 84 (35%) who were 3 months age. Our results are compatible with mean age of 7.5 months and 4.2 ± 2.6 months reported from South Korea and Argentina, respectively[3,15].

Another study from Karachi, Pakistan, looking into rickets in pneumonia reported rickets in infants

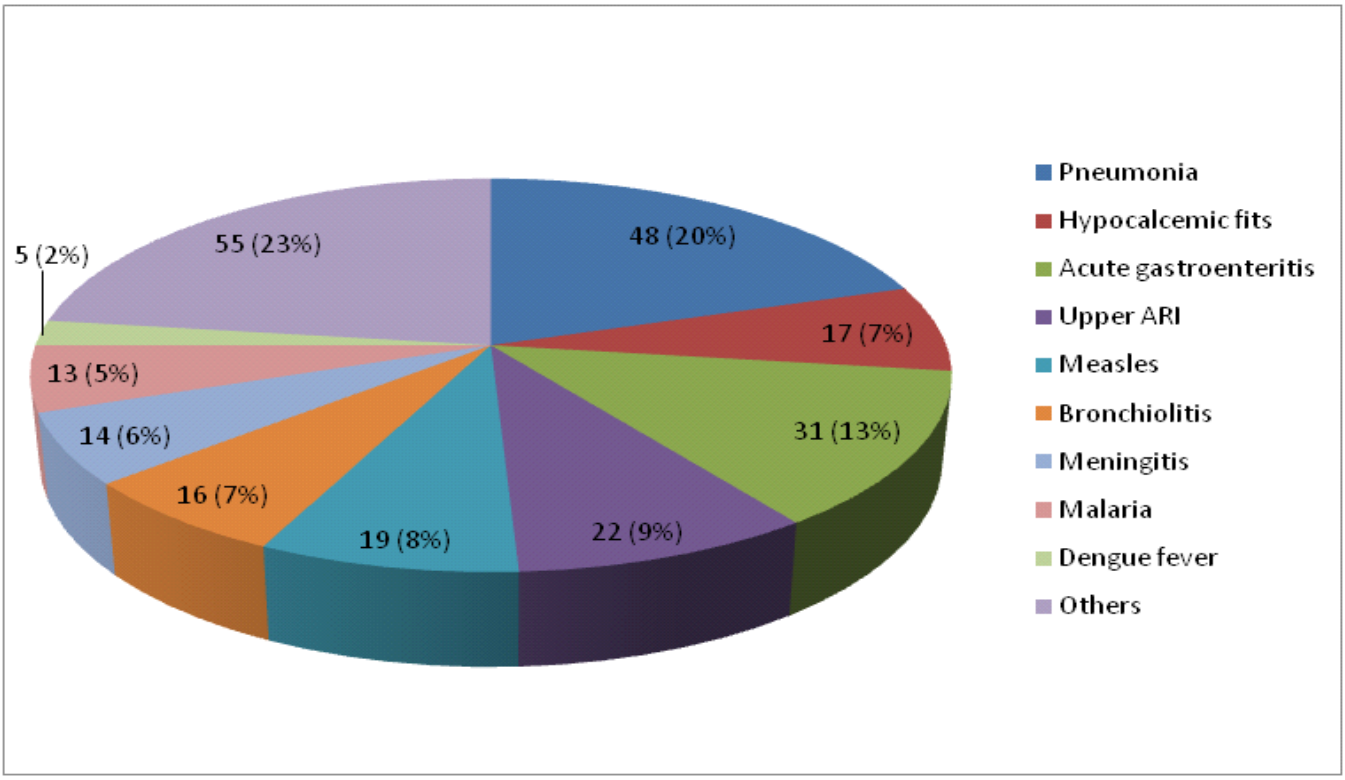

Fig. 1. Reasons for admissions of patients diagnosed with rickets

as young as 2 month age with 61.3% of their study subjects falling in the age group of 2-12 months[5]. India too, has reported 11.11% patients of NR who were <6 months of age including 7% who were ≤3 months age but in their study, a maximum of 44.44% patients of rickets were contributed by a higher age group of 1-2 years, as compared to <1 year in our study which is surprising in the wake of similarities in environment, culture, eating habits, social parameters and disease prevalence among the two countries[16]. In addition to India, several countries including Japan, Nigeria, Johannesburg, Spain, Canada and Polynesia have also documented results contrary to ours showing nutritional rickets to be most common in infants and toddlers within the age range of 1-3 years[3], the mean age being 20 months in Johannesburg. The probable reasons for this lower age at diagnosis in our patients in contrast to others may be variable age ranges of the subjects included in these studies. In addition, these may be because of differences in environmental, social and cultural factors such as inadequate dietary management and availability of pure food, a lot of food taboos, evading sunlight for various reasons, fortification of food with vitamin D, more so in our country than others.

Though most of these factors do not apply for difference of results from India, one reason that might explain this discrepancy is the fact that the age at presentation of nutritional rickets is affected by its underlying cause, with Vitamin D deficiency characteristically presenting between 3 and 18 months of age and calcium deficiency presenting at a later age of 1-16 years. India, Nigeria and Bangladesh are some of the countries who have identified calcium deficiency rather than vitamin D deficiency as the predominant cause of nutritional rickets[3]. But variation in ages at diagnosis of rickets cannot be explained solely by hypocalcaemia or hypovitaminosis D as the cause of NR since there are reports from Northern India showing vitamin D deficiency rickets in older children and adolescents, more so in girls 10-13 years of age, contrary to their acknowledgement of low calcium intake as the main cause of NR. Similarly Johannesburg, have identified vitamin D deficiency rickets as most common cause of NR, but the mean age was 22 months[3]. In our study also, vitamin D deficit was the main reason for rickets being present in 100% of the study subjects in whom serum vitamin D levels could be done. This is comparable to another recent report from a public sector hospital of Karachi which shows the frequency of vitamin D deficiency in 75% of the cases with rickets[17]. In our case, the lower age of presentation is in accordance with the literature, but the frequency of lower age is definitely higher as compared to the rest of the literature as discussed above[3,6,18] and mean levels of vitamin D are lower than other reports from around the world except for South Korea which reported a deficit of vitamin D in 97% of patients similar to our results[3,14,15]. Another characteristic of nutritional rickets caused by vitamin D deficiency mentioned in literature is its predilection for temperate countries[3], and that too is appropriate for our study subjects, Pakistan being a temperate country. However, what cannot be explained is the predominance of calcium deficient rickets in India and Bangladesh in spite of them being temperate countries too. Two other studies from Pakistan carried out on all age groups, mostly adults, documented normal vitamin D levels in[15] 3-21.8% of their study subjects only[19,20] conforming to our results and, thus, indicating similar disease burden in all ages.

Further analysis of the severe deficiency in our study revealed that it was most frequent in the youngest age group of 1-3 months and the association was shown as significant by statistical analysis (Table 2). This association is contrary to what is reported in literature[14,20]. While nutritional rickets has persisted in underdeveloped countries, the high income countries have also witnessed its resurgence as already mentioned. This has been attributed to incursion of immigrant populations especially from South Asia, Africa and Middle East[3,7,13]. Data analysis of last few decades in England have shown a disproportionately higher frequency of South Asians and blacks among children with rickets contrary to a significant decline in whites[7]. This effect of ethnicity demonstrating increased possibility of developing vitamin D deficiency rickets was documented by several researchers mainly among children of immigrants from Middle East especially South Asians mostly originating from India, Pakistan and Bangladesh[3,7,13]. Higher prevalence of vitamin D deficiency among children of Pakistani

descent has also been reported by Denmark, Norway and Spain[7]. This provides food for thought about the possible role of genetics in addition to environment as risk factor for development of vitamin D deficiency rickets. The absence of any gender preference in our study subjects with males and females sharing 50% of the cases each is similar to reports of 54-61% from other countries[6,14-17].

Though the incidental diagnosis of Rickets in patients during evaluation for other illnesses has been documented by Krishan et al. also[16], their frequency of 48.1% is much lower as compared to our study where almost all (85%) the rickets was diagnosed incidentally. Most common reason for admission of these patients was pneumonia, the result being similar to other study in literature[15]. It not only remains as one of the most neglected dietary deficiencies in regards to its timely diagnosis and treatment but is affecting every section of the population regardless of the age and gender despite the fact that it can be prevented and treated very easily and effectively[19,20]. This has been successfully demonstrated by the United Kingdom and Turkey by achieving a drastic reduction in vitamin D deficiency and rickets by simple manoeuvres including public education about the disease and ensuring availability and supplementation of neonates with oral vitamin D using their primary maternal and child health care systems[3,7,13]. This is high time that we increase the awareness of our population in general and physicians in particular regarding the amplitude of the problem associated with the disease and start supplementing our infants with vitamin D at an early age.

We know that development of NR is influenced by an array of local, traditional and may be genetic factors. Therefore we need further and broader research to identify these factors in order to effectively do away with NR. Our study is limited by the fact that it was carried out in a government sector hospital of Karachi on admitted patients only. Also, the population reporting to this hospital belongs mostly to the lower socioeconomic strata and, thus, creating an economic bias. Therefore, the results cannot be generalised to the whole population of Pakistan. Certain variables like the vitamin D status of mothers, dietary habits of the subjects, their nutritional status and exposure to sunlight may confound the age of the subjects at which they develop vitamin D deficiency and, thus, rickets but we did not consider those since our objective was to determine the age at which NR is diagnosed, irrespective of the causative factors. To determine a more comprehensive conclusion, further studies are warranted.

Moreover, we did not look into the fact that there is a uniform recommendation that all breastfed infants should receive 400 IU of vitamin D. This aspect should be related to vitamin D deficiency in early age presentation of rickets and also a co-relation with vitamin D deficiency in the mother. This study did not look into the nutritional status of the mother, but since most of them belong to the low socioeconomic class, it can be assumed that they are malnourished. We were unable to document vitamin D levels in the mothers which can be an important precursor for vitamin D deficiency in the baby. Future studies, multicentre studies will cover this aspect. Hence, studies should be conducted on the use of vitamin D in pregnancy and its impact on the foetus and infants.

Despite international and local recommendations, patients are not receiving the vitamin D supplementation before the age of six months which needs to be investigated. We recommend education of masses and doctors using various means including the media and mosques to increase awareness regarding the deficiency of vitamin D and its early identification, its consequences and prevention including the exposure to sunlight and appropriate diet.

Increasing the availability of laboratory test for vitamin D levels, ensuring its availability at all times at least for the departments of paediatrics and obstetrics of government sector hospitals and at reduced cost in private laboratories will be of benefit. We further recommend studies to assess the vitamin D levels of mothers during pregnancy, supplement them and study the effects of their supplementation on their neonate. The ministry of health should be urged to fortify required food products with vitamin D.

Conclusion

We conclude that the frequency of severe deficiency was highest in the youngest age group of 1-3 months and the association of age at diagnosis of NR with vitamin D levels was shown as statistically significant. Most (85%) cases of rickets were diagnosed incidentally showing lack of awareness of our general public and general practitioners regarding the burden and signs of rickets.

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