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Genetic Factor Plays Apart in the Causation of Vitamin D Deficiency Rickets at Riyadh

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Abstract: The objective of this work to explore some factors leading to rickets in children in Riyadh with special reference to socio-economic status,the type of feeding, vitamin D administration,exposure to sun light, sex difference and ABO blood grouping of the affected infants and children. The subject studied constituted 120 rachitic infant and children representing different socio-economic districts who were attending the outpatient clinics at hospital of pediatric, King Saud Medical Complex, Saudi Arabia. They were randomly chosen. Their ages ranged between 6 month and 2 year (72 males and 48 females) in comparison to normal sex and age matched healthy controls. A questionnaire was administered to all mothers of the studied group including personal and socio-economic data, history of consanguinity, complaint, the type of feeding and history of vitamin D administration. A complete examination of the infants and children was performed with special stress on the rachitic manifestations as enlargement of the head, size of anterior fontanel, eruption of teeth and skeletal deformity. Diagnosis of vitamin D deficiency rickets was based on the usual clinical criteria and biochemical findings including low serum vitamin D, calcium, phosphorus and high serum alkaline phosphatase. All infants were free from any other pathological conditions (acquired or hereditary) which are known to be associated with ABO blood groups as diabetes mellitus. Blood groups determination (ABO typing), serum vitamin D, calcium, phosphorus and alkaline phosphatase was measured. A significance difference was found between rachitic cases and control as regards their socio- demographic data ($P<0.01$) and 55% of the rachitic cases came from slum areas and it was found that 76% of rachitic cases gave history of consanguinity. Statistically blood group A was predominantly affected whether in males or females infants compared to control group. As regards to some social factors of rickets, it was found that 73% of rachitic cases with lack exposure to sun light and 19% of rachitic cases are living in open house. As regards the type of feeding 71% of the rachitic infants and children were breast fed, 18% had received vitamin D therapy. The most common signs found were 3o% delayed closure of anterior fontanels, 28% enlargement of the head; the complications found on examination were 26% gastroenteritis. Regarding association between vitamin D deficiency and different predisposing factor, it was observed from our results that most predisposing factor for vitamin D deficiency rickets was genetic liability followed by exclusive breast feeding with low vitamin D supplement, less exposure to sun light, negative history of calcium supple ment and low socio-economic status represented by increased family size and low family income. Our study revealed many risk factors for rickets in infant and children indicating a multi-factorial nature of the disease.

Key words: Rickets · Vitamin D deficiency · Alkaline phosphatase · Calcium and phosphorus

INTRODUCTION

Rickets may be regarded as one of the diseases in which a genetically transmitted defect is manifested under adverse environmental conditions as may be found in exclusive or prolonged breastfeeding [1]. Nutritional rickets is gaining the attention of public health professionals and individual clinicians worldwide as the disease remains an endemic problem in many developing countries and has re-emerged in a number of developed countries, where it was thought that the disease had been almost eradicated [2]. In Saudi Arabia, vitamin D deficiency and rickets continues to be a public health problem despite abundant all year sunshine in many of

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the regions. The cause of rickets in developing countries remains an enigma. Limited sunlight exposure, exclusive or prolonged breastfeeding without vitamin D supplements, gestational vitamin D deficiency and additional factors including genetic factors may have a key role in the pathogenesis of the disease [1]. Infants are particularly at risk especially if they are exclusively breast fed. While breastfeeding is the recommended method of infant feeding and provides infants with necessary nutrients and immune factors, breast milk alone does not provide infants with an adequate intake of vitamin D. Most breastfed infants are able to synthesize additional vitamin D through routine sunlight exposure. Rickets among breastfed infants in the United States caused researchers to take another look at whether all breastfed infants were getting adequate vitamin D [3].Vitamin D deficiency rickets among breastfed infants is rare, but it can occur if an infant does not receive vitamin D supplement or from inadequate exposure to sunlight [4]. Jonxis *et al*. [5] studied the aminoaciduria of vitamin D deficiency rickets and found that some members of the families of rachitic infants were also excreting abnormally large amounts of amino acids. They have suggested that there might be a hereditary factor in the pathogenesis of the disease. The possibility received additional support when sex differences in infants with nutritional rickets were found by Childs [6] and El Kholy *et al*. [7]. We do encourage breast feeding for the first months of life but also we recommend vitamin D supplementation from the first month of life in order to prevent the genetic susceptibility especially to male to nutritional rickets.

MATERIALS AND METHODS

This was case control study,the subject studied constituted 120 Saudi child representing different socio-economic districts who were attending the outpatient clinics at hospital of pediatric, King Saud Medical Compound, Saudi Arabia. They were randomly chosen. Their ages ranged between 6 month and 2 year (72males and 48 females) in comparison to normal sex and age matched healthy controls (60). This study was carried out from October 2010 to January 2011.

Methods: A questionnaire was administered to all mothers of the studied group including:

Personal and Socio-Economic Data: Including, name, age, sex, address, education and occupation of both the mother and the father and family income, history of consanguinity, also questions about some social factors including exposure to sun light.

Dietetic History: Including: the type of feeding, breast, artificial or both, solids and history of vitamin D administration for both infant and mother.

Medical History: A questions related to any manifestation of rickets and history of complication.

Complete Examination: Of the infants and children was performed with special stress on the rachitic manifestations as enlargement of the head, size of anterior fontanel, eruption of teeth, any skeletal deformity and rosary beads, etc. All infants were healthy with normal weight for their ages. They were free from any other pathological conditions (acquired or hereditary) which are known to be associated with ABO blood groups as diabetes mellitus, leprosy, congenital heart disease... etc.

Investigations: Diagnosis of Vitamin D deficiency rickets was based on the usual clinical criteria and low level of serum calcium, phosphorus and 25-hydroxy vitamin D (25(OH)D) and high serum alkaline phosphatase: Blood samples were collected and were analyzed by atomic absorption spectrophotometer (AAS) to measure Serum calcium and phosphorus[8]. Serum 25-hydroxy vitamin D (25(OH) D) level was assessed by Jean-Claude Alvarez and Philippe De Mazzancourt [9]. Serum alkaline phosphatase was measured [10]. Blood groups determination (ABO typing) using the agglutination method (slide technique) [11].

Statistical Analysis: Data were expressed as mean ± SD and were analyzed statistically using SPSS package; collected data was statistically analyzed using suitable statistical tests (chi square, T-test, correlation coefficient, odd's ratio). The P value was considered significant at ($P \leq 0.05$) [12].

RESULTS

The study was conducted on 120 rachitic cases whose ages ranged from 6 months and 24 months (72 males and 48 females) with a mean age 15. 1±3.22 of months. It was observed from the table that the males represented 60 and 40%) of the females.As regards to their socio- demographic data(Table 1): 55% of the rachitic cases came from slum areas, while 27% came from rural areas and 18% from urban areas. It was observed from the table that most of the rachitic cases (71%) their families size >2 persons. As regards the educational status, (36 and 49%) of fathers and mothers of rachitic children were illiterate, respectively. On describing the occupation: 38% of fathers of rachitic child were manual

Table 1: Socio–Economic characteristics of the studied sample

	Cases (120)		Control (60)		
Variable	No	%	No	%	P value
Age (months)	6-24				P≤ 0.01
Mean	15.1± 3.22				
Sex:					
Male	72	60	36	60	
Female	48	40	24	40	
Residence:					
Slum areas	66	55	11	18	
Rural areas	32	27	13	22	
Urban areas	22	18	36	60	
Family size:					
≤ 2nd person	35	29	35	59	P≤ 0.01
> 2nd person	85	71	25	41	
Father education:					
Illiterate	44	36	5	9	P≤ 0.01
Preparatory & Secondary	38	32	19	31	
University & Postgraduate	38	32	36	60	
Mother's education:					
Illiterate	59	49	10	17	P≤ 0.01
Preparatory & Secondary	35	29	17	28	
University & Postgraduate	26	22	33	55	
Father occupation:					
Manual	45	38	11	19	P≤ 0.01
Employee	44	36	13	22	
Professional	31	26	36	59	
Mother's occupation:					
Working	48	40	47	79	P≤ 0.01
Non Working	72	60	13	21	
Family income:					
Sufficient and saving	36	30	36	60	P≤ 0.01
Sufficient	23	19	14	24	
Insufficient	61	51	10	16	
History of consanguinity:	92	76	21	35	P≤ 0.01

and 36% were employees. On describing the occupation of children's mothers about (60%) of mothers of rachitic child were house wives with 51% insufficient family income and it was found that 76% of rachitic cases gave history of consanguinity. A significance difference (P<0.01) was found between rachitic cases and control as regards their socio demographic data. Table 2 showed distribution of studied group according to some social factors associated with rickets, it was observed from the table that 73% of rachitic cases with history of lack exposure to sun light comparing to 15% of control, while 66% of rachitic cases with history of complete wrapping of child and 19% of rachitic cases are living in open house.

As regards the type of feeding (Table 3), 71% of the rachitic infants and children were breast fed, 12% of them were bottles feeding and breast, 8% of them were bottles feeding only 6% of them were breast, bottles feeding and solid bottles feeding s and 4% of them were solids only. It was observed from the table, 18% had received vitamin D therapy. It was observed from the Table 4, the most common signs found, delayed closure of anterior fontanelle 30%, enlargement head 28%, gross motor delay 13%, skeletal deformity 11%, Marfan's sign 9%, delayed eruption of teeth 4%, rachitic rosary beads 2%, umbilical hernia 2% and chest deformity 1%. Table 5 showed distribution of studied group according to the complications, It was observed from the table that

Table 2: Distribution of the studied group according to some social factors associated with rickets

	Rachitic cases (120)		Control (60)		
Factors	No	%	No	%	P value
≤30 minutes exposure to sun light / day	88	73	9	15	p< 0.01
≥30 minutes exposure to sun light / day	32	27	17	29	
Living in open house	23	19	43	71	
Complete wrapping of child	79	66	17	29	

Table 3: Distribution of the studied group according to type of feeding

	Cases		Control	
Type of feeding	No	%	No	%
Breast feeding only	85	71	24	40
Bottles and breast feeding	14	12	14	23
Bottles feeding only	10	8	11	18
Breast feeding, bottles feeding and solids	7	6	10	17
Solids only	5	4	1	2
Vitamin D supplements	22	18	38	63

Table 4: Distribution of the studied group according to the manifestation

Manifestation	Rachitic	%
Delayed closure of anterior fontanel	36	30
Enlarged head	34	28
Gross motor delay	16	13
Skeletal deformity	13	11
Mar fans sign	11	9
Delayed eruption of teeth	5	4
Rachitic rosary beads	2	2
Umbilical hernia	2	2
Chest deformity	1	1

Table 5: Distribution of the studied group according to the complication

The complication	Number	%
Castro – enteritis	31	26
Bronchitis	29	24
Dwarfism and residual deformities of bones	23	19
Convulsion	20	17
Without complication	17	14
Total	120	100

Table 6: Blood groups distribution in rachitic patients compared with controls

	Cases		Controls	
Blood group	No	%	No	%
A	48	40	23	38
B	22	18	11	19
AB	14	12	3	5
O	36	30	23	38
Total	120	100	60	100
P < 0.001	(Significant)			

Table 7: Distribution of the studied sample according to blood analysis

	Rachitic cases		Control		
Items	No.	%	No.	%	Chi square p
25(OH)D					P≤ 0.0
≤ 15ng / ml	96	80	17	29	
> 15ng / ml	24	20	43	71	
Alkaline phosphatase					
≤ 25 K,U	35	29	40	66	P≤ 0.0
> 25 K.U	85	71	20	34	
Calcium					
≤ 9 mg /dl	82	68	16	28	P≤ 0.0
>9 mg /dl	38	32	44	72	
Phosphorus					
≤ 3 mg/dl	92	77	13	22	P≤ 0.0
> 3 mg/dl	28	23	47	78	

Table 8: Values of vitamin D, alkaline phosphatase and calcium in different blood groups in studied group.

	Blood group							
	A		B		AB		O	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD
25(OH)D	8.14	5.01	11.47	6.03	10.16	5.22	12.06	5.31
Alkaline phosphatase	27.33	18.13	48.43	17.01	47.66	16.11	50.17	18.07
Calcium	7.23	3.19	6.54	3.22	8.22	4.37	9.82	5.52
Phosphorus	2.26	2.88	2.59	1.27	2.22	3.07	2.52	1.02

P ≥ 0.05 (Non significant difference)

Table 9: Correlation coefficient between manifestation of vitamin D deficiency and values of vitamin D, alkaline phosphatase and calcium and phosphorus of the studied groups

Variable	Correlation coefficient	P
Vitamin D	- 0.5 2	< 0.05
Alkaline phosphatase	0.7	< 0.05
Phosphorus	-0.4	< 0.05
Calcium	-0.3	< 0.05

Table 10: Association between vitamin D deficiency and different predisposing factor

Predisposing factor	Odd' s ratio
Genetic liability	5.1
Exclusive breast feeding without vitamin D supplementation	-4.2
Less exposure to sun light.	-3.6
Negative history of calcium supplement	3.0
Mothers education	-2.7
Family income	-2.0
Family size	1.7

the most common complications found were: 26% gastroenteritis, bronchitis 24%, 19% dwarfism and residual deformities of bones and Joints, 17% convulsion while 14% of the cases of the rickets without complication. Table 6 showed the number of those of blood group A were 80 cases with percentage of 40% including both males and females. The incidence of rachitic affection among those of blood group 0 ranked the second and represented 36 cases with percentage 30%. Rachitic individuals of blood group B ranked the third and represented 22 cases with percentage 18%, the last affected blood group of the rachitic was the AB group which represented 14 cases with a percentage 12%. Statistically blood group A is predominantly affected whether in males or females infants compared to control group. Table 7 showed distribution of studied group according to blood analysis, it was observed from the table that there was high percentage (80%) of rachitic

cases with serum level 25-hydroxy vitamin D (25(OH)D) less than 15ng /ml, 71% of rachitic cases with serum level alkaline phosphatase more than 25 k.u and there was high percentage (68%) of rachitic cases with serum level calcium less than 9 mg /dl and high percentage (77%) of rachitic cases with serum level phosphorus less than 3 mg /dl. A significance difference was found between rachitic cases and control as regards blood analysis ($P<0.01$). No statistically significant difference was found between different blood groups as regards to values of vitamin D, alkaline phosphatase, calcium and phosphorus in rachitic cases (Table 8). Table 9 showed correlation coefficient between manifestation of vitamin D deficiency and values of vitamin D, alkaline phosphatase, calcium and phosphorus of the studied groups. It was observed from the Table 9, a highly negative correlation coefficient was found between the level of vitamin D, calcium as well as phosphorus and manifestation of the rickets ($p<0.05$). Also a positive correlation coefficient was found between the level of alkaline phosphatase and manifestation of the rickets ($p<0.05$). Table 10 showed association between vitamin D deficiency and different predisposing factor, regarding association between vitamin D deficiency and different predisposing factor, it was observed from the table that most predisposing factor for vitamin D deficiency was genetic liability (Odd's ratio 5.1) followed by exclusive breast feeding with low vitamin D supplement(Odd's ratio -4.2), less exposure to sun light (Odd' s ratio-3.6), negative history of calcium supplement (Odd's ratio 3.0) and low socio-economic status which represent by mother education (Odd's ratio-2.7), low family income (Odd's ratio-2.0) and family size (Odd's ratio 1.7).

DISCUSSION

During the last 10 to 20 years rickets due to vitamin D deficiency has almost disappeared from the United States and from many countries of Western Europe [3]. However, nutritional rickets still exists with high prevalence in developing countries [13]. This work has demonstrated many epidemiological aspects of rickets in Riyadh. One of the important epidemiological aspects of nutritional rickets found in this study was that most of the rachitic cases with low socioeconomic status and 55% of them came from slum areas, where poverty, ignorance and illiteracy predominate [14]. We have found a high incidence of rickets among male infants, the male sex predominance found in our study, is in accordance with previous study of El Kholy *et al.* [7]. Childs [6] reported that one of the facts of life is the greater susceptibility to disease and to early mortality of the human male. The reasons for these discrepancies are unknown but might be thought in an analysis of differences between the sexes in development and in genetic constitution. The Y chromosome is considerably smaller than the X given the female a 4-5% quantitative superiority in genetic material. So, the differences between normal male and female might exit because the female has two such genes while the male has one, expression of this difference might be in susceptibility to vitamin D deficiency rickets. In other word, the presence of a normal allele in the female protects her against the ravages of a mutant which, unopposed by any homologue in the male, does harm. Thus rickets may be regarded as one of the diseases in which a genetically transmitted defects is manifested under adverse environmental conditions as may be found in malnutrition. From the present study, it has become clear that some of the factors play a more critical role than others in causing nutritional rickets. These factors have been quantified.

From the present study, it was found that blood group A is predominantly affected whether in males or females rachitic infants compared to control group, the possibility of blood groups influencing predisposition to certain diseases has always been a subject of interest. This finding adds more support to the study of El Kholy *et al.* [7] who revealed that statistically blood group A is predominantly affected whether in males or females rachitic infants compared to control group. Several studies in the last few years have shown that certain diseases of the alimentary tract to diseases of the mind are associated with particular blood groups more frequently than would be expected by chance. These observations suggest a causal relationship between a particular disease and the blood group with which it is associated [15, 16]. In our study, we did find an association between blood group A and nutritional rickets. We assume that since blood groups are inherited so genetic factors could play a part in the causation of the particular disease vitamin D deficient rickets in our case, with which they are associated. The possibility that heredity might be a factor in the pathogenesis of vitamin D deficiency rickets is supported by Dioxides *et al.* [17] who reported a continuing aminoaciduria twelve weeks after biochemical and radiological healing in some cases of vitamin D deficiency rickets. They also demonstrated an abnormally high excretion of amino acids and of phosphorus in many of the parents of the rachitic infants studied. Recently, Holick [18] reported that heredity might be a factor in the pathogenesis of vitamin D deficiency

rickets. Also, Shawky *et al.* [19] suggested that a persistent biochemical defect, which might be hereditary, is present in those infants with nutritional rickets. As regards the type of feeding: 71% of the rachitic infants and children were breast fed, this result came in agreement with study of Balasubramanian and Ganesh [20] who revealed that most of the rachitic children were breast-fed, as breast-feeding rates increase, the incidence of vitamin D deficiency rickets is also expected. This finding adds more support to the study of Ponnapakkam *et al.* [21] who revealed that most of the rickets patients were breast-fed. The increase in the practice of breast-feeding, associated with the belief that "breast is breast" and that breast milk does not require supplementation because it is a baby's "perfect food" may lead to decreased 25-hydroxy vitamin D(25-OHD) intake from other sources and thereby causing rickets [22].

Our result revealed that 18% only of all our rachitic infants received vitamin D, this result came in agreement with study from China [23] had observed that breast-fed infant with insufficiency intake of vitamin D supplement especially those living in parts of the country where inadequate exposure to sunlight. Hollis and Wagner [24] noticed that although breast milk is adequate for growth and bone mineralization in the first year of life but vitamin D supplementation must be necessary for breast -fed infants. We do encourage breast feeding for the first months of life but also we recommend vitamin D supplementation from the first month of life in order to prevent the genetic susceptibility especially to male to nutritional rickets. It was observed from our result that the percentage of the rachitic cases were received vitamin D supplementation was low compared to the control, which denotes the low level of health education among the mothers. Health education can be carried out through mass media and health workers must be well established in this respect. Our result revealed that 8% of the rachitic infants and children were bottle feeding only this is obvious due to the expensive formulas sold in comparison to breast milk [25]. Our results revealed that 73% of rachitic cases with history of lack exposure to sun light and 66% with history of complete wrapping of child and 19% of rachitic cases are living in open house. This finding adds more support to the study of Majeed *et al.* [26] who found lack of exposure to sunlight due to complete wrapping of the child play more important role for contribution of nutritional rickets. The most common signs found in our rachitic infants were delayed closure of anterior fontanels, enlargement of the head circumference and skeletal deformity, the investigation support that the most rachitic cases with elevation serum level of alkaline phosphatase, low serum level of 25(OH) D, calcium as well as phosphorus, this is in accordance with previous study of Balasubramanian and Ganesh [20] and the present results are in agreement with the results reported by Ladhani *et al.* [27] and Biswas *et al.* [28]. Consequently we do recommended complete clinical examination to every infant coming to the outpatient clinics in order to detect early manifestations of vitamin D deficient rickets. So, we advice the routine measurement of skull circumference which must be an essential part of the examination and was found to be an important tool together with the elevated level of serum alkaline phosphatase in the diagnosis of active rickets.

Regarding association between vitamin D deficiency and different predisposing factor, it was observed from Table 10 that most predisposing factor for vitamin D deficiency was genetic liability represented by male predominant, blood group A is predominantly affected whether in males or females rachitic and high percent of rachitic cases gave history of consanguinity followed by exclusive breast feeding with low vitamin D supplement, less exposure to sun light,, negative history of calcium supplement and low socio-economic status represented by increased family size and low family income. Our study revealed many risk factors for rickets in infant and children indicating a multi-factorial nature of the disease. Similar findings were obtained by Thacher *et al.* [29] and Dawodu *et al.* [30], where their study revealed many risk factors for rickets in infant and children indicating a multi-factorial nature of the disease. The most important revealed risk factors were prolonged breast feeding without vitamin D supplement, calcium insufficiency and less exposure to sun.In this environment, VDR genotypes may predispose to rickets by increased frequency of Fallele [31]. The environment and genetic predisposition have to be accounted for in design of prevented measures rather than using European or American recommended dietary intake for calcium and vitamin D.

CONCLUSION

Nutritional rickets is a multi-factorial condition. However, several factors seem to make important contributions. Among these, genetic liability, prolonged breast-feeding without vitamin D supplementation, low socio-economic status and lack of exposure to sunlight. So the genetic and environmental factors interact in clinical rickets and much effort should be done in order to combat it. Most geneticists believe that genetic factors

are involved in susceptibility to many human diseases; nutritional rickets may be one of these diseases. Our study gives added support for that belief. It is suggested that a national campaign to promote awareness of the risks of vitamin D deficiency, particularly among susceptible populations be done to eliminate rickets as a cause of morbidity.

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