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Research Article

Evaluation of Some Cardiac Functions among Children with Vitamin D Deficiency Rickets

Abstract

Vitamin D deficiency rickets (VDDR) is commonly recognised disease in Egypt. The most striking biochemical finding in this illness is hypocalcaemia which may affect ventricular contraction. This study was a prospective hospital based study aiming to evaluate some cardiac functions among children with VDDR by Echocardiography.

Patients and Methods: Patients: The included 100 patients (Group 1) with VDDR in addition to control group (Group 2) which included 50 healthy children. Methods: all cases were subjected to a thorough history, full clinical examinations and investigations which include: serum calcium, phosphorus, alkaline phosphatase, 25(OH) vitamin D, parthormone, chest x ray, electrocardiogram and echocardiography to measure [left ventricular functions systolic function which include(ejection fraction% (EF%), fraction shortening% (FS%) left ventricular end diastolic diameter(LVEDD) and left ventricular end systolic diameter (LVESD)].

Results: EF%&FS% were significantly lower while LVEDD & LVESD were significantly higher among studied VDDR cases (Group 1) when compared with control (Group 2). These echocardiographic parameters were improved with treatment with vitamin D and calcium. Conclusions: children with VDDR have a significant impairment in left ventricle systolic functions which improved with appropriate treatment.

Introduction

Vitamin D deficiency rickets (VDDR) remains prevalent in developing regions of the world and ranks among the 5 most common diseases in children [1]. The incidence of rickets among Egyptian children during the first 2 years was reported to be 12-31.1% [2]. VDDR is common in Egypt as a result of both inadequate diet and inadequate exposure to ultraviolet light. VDDR may be clinically either with rickets or symptoms of hypocalcaemia .In general the latter symptoms occur in young patients under 2 years of age or adolescents, whilst older pre-pubertal children are more likely to have rickets, but both rickets and symptomatic hypocalcaemia can occur together [3]. Despite high incidence of VDDR among Egyptian children no single published Egyptian study tried to evaluate the effect of VDDR on the heart. On the other hand, only few studies in literatures tried to evaluate the effects of VDDR on the heart and most of these studies in the form of case report. The aim of this study is to assess some cardiac functions in children with VDDR.

Patients and Methods

Patients

This is *cross sectional prospective hospital based study*. It included 100 children with VDDR (Group 1). There were 68 boys and 32 girls. In addition, 50 apparently healthy age and sex matched children were studied as a control (Group 2). They were 37 boys and 13 girls. The study was conducted during the period from March 2008 to February 2009. Both patients and controls were recruited from *Paediatric Outpatients Clinics and Paediatric Emergency Department* in Assiut University Children Hospital, Egypt.

The diagnosis of VDDR was based on a combination of clinical, radiographic and biochemical features of VDDR [1]. Clinical rickets was defined if there are 2 or more of the following signs: rosary beads, craniotabes, frontal bossing, Harrison's sulcus with pigeon chest, wide anterior fontanel, widening of epiphysis, bowing of legs, delay dentition,

and double malulous [4]. Radiological evidence for rickets included two or more of the following signs: generalized osteopenia, fraying and cupping of the distal ends of the radius or ulna, or widening of the costochondral junction [5]. biochemical features of VDDR include: low or normal serum calcium concentration, low serum phosphate concentration, elevated alkaline phosphatase activity with or without raised parthhormone. Vitamin D deficiency was defined as: serum 25 (OH) vitamin D level less than 10 ng/mL [1].

Inclusion criteria were

- 1) Age range 6 months to 2 years.
- 2) Clinical, radiographic and biochemical features of VDDR.
- 3) No treatment with vitamin D (except prophylactic supplementation dose, 400 IU/day).
- 4) No medications interfering with calcium-phosphate metabolism e.g anticonvulsants.

Exclusion criteria were

- 1) Previous history of heart disease or any other condition that might affect cardiac functions.
- 2) History of prematurity or intrauterine growth retardation.
- 3) Renal, liver, intestinal, or central nervous system disease.
- 4) Family history of hereditary forms of rickets.
- 5) Treatment with vitamin D or vitamin D supplements above 400 IU/day.
- 6) Malnutrition and anaemia.

The study protocol was approved by the ethical committees of Assiut University Children Hospital, Egypt. Written informed consents were obtained from the parents of both patients and controls.

All cases were subjected to the following:

- **History:** Onset, course, type of feeding, previous history of rickets, vitamin D supplementation, exposure to sun light, weaning and medication.

Clinical examination:

- Anthropometric measurements (weight, length/height and head circumference).
- Signs of rickets: delayed motor development, rosary beads, delayed closure of the anterior fontanel, craniotabes and broadening of end of upper & lower limbs.

Radiological examination:

- X ray of wrist for detection of cupping, fraying, flaring and osteopenia.
- Chest X ray for detection of cardiothoracic ratio (C/T ratio) .Cardiomegaly was considered if C/T ratio > 50% [6].

Laboratory tests

- Serum calcium (Reference range: 8.8 -10.8 mg/dL).
- Serum phosphorus (Reference range: 3.8 - 6.5 mg/dl).
- Serum alkaline phosphatase (Reference range: 145 - 420 U/ L).
- Serum 25(OH) D (Reference range: 10 - 53.3 ng/ mL).
- Intact parthhormone level (Reference range: 9 - 65 pg / mL).

Serum calcium, phosphate and alkaline phosphatase levels were measured by standard methods. Serum intact PTH level was measured by a two-site immunoradiometric assay. Serum 25 (OH) vitamin D level was measured by competitive binding RIA [1,7].

Electrocardiographic measurements

Resting 12-lead electrocardiograms (ECG) studies were performed for all rachitic cases and interpreted in accordance with the patient's age and sex, and the QT segment was corrected for heart rate (QTc) [6].

Echocardiography

After improvement of acute illness of studied cases. All cases and controls underwent echocardiographic studies using M-mode, two-dimensional, and Doppler techniques, using commercially available phased array system employing a 4 and 7 MHZ transducer respectively (Magic bright 2, Vivid 3, Vingmed-Tech). Measurements were performed using the machine's incorporated analysis package. The following measurements were taken on all patients and control:

1- Left ventricular systolic functions

- Left ventricular end diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular posterior wall thickness LVPWT; interventricular septal wall thickness IVSWT, interventricular septal wall thickness/left ventricular post wall thickness I/L.
- Percentage of fractional shortening (FS) :LV FS% was calculated using the following formula [6]:

$$FS = \frac{EDD - ESD}{EDD} \times 100$$

Where, EDD is the end diastolic diameter of the left ventricle and ESD is the end systolic diameter of the left ventricle [6].

- Ejection fraction (EF): measured from the "cubed equation" [6]:

$$EF = \frac{EDD^3 - (ESD)^3}{(EDD)^3} \times 100$$

- Left ventricular mass (LV mass) and left ventricular mass index. It is performed by using LVMI calculator

2- Left ventricle diastolic function E/A: using the E/A ratio of mitral flow by pulsed wave Doppler across the mitral valve.

The recordings and measurements were obtained in accordance with the recommendations of the American Society of Echocardiography [8].

Treatment

Cases with VDDR were treated with intramuscular injection of vitamin D (cholecalciferol) (600 000 IU) once and oral calcium for 2 weeks followed by oral maintenance dose of vitamin D 400 unit/day for 6 months. In urgent situations, such as convulsions, calcium was initially administered intravenously as calcium gluconate [9,3].

Statistical analysis

Analysis was carried out using SPSS (version 16). The numerical data were represented as mean \pm SD. For comparison of the two groups, Student's t-test was used for parametric data and the Mann-Whitney U-test was used for non-parametric data. Multiple groups were compared using the ANOVA test. Linear correlations were performed by Spearman's or Pearson's test. For all tests, the difference was considered significant if the probability (P):

P < 0.05 = significant S

P < 0.01=highly significant HS

P < 0.001=very highly significant VHS

Results

The clinical presentation of cases in group 1 was as follows: 44 cases presented with respiratory tract infection, 26 cases with gastroenteritis, and 18 cases with convulsion and 12 cases with delayed motor development.

Table 1 shows the demographic and anthropometric characteristics of cases in group 1 compared with group 2. No statistically significant difference between group 1 and group 2 regarding age, residence, weight, height /length and head circumference.

Chest x ray of the studied cases showed increase of cardiothoracic ratio > 50% in 14 cases, while ECG showed T wave abnormalities in 4 cases and prolonged QT interval in 6 cases.

Table 2 shows the biochemical data of cases in group 1 compared with group 2. Cases with VDDR had significantly lower level of serum calcium, phosphorus and 25(OH) vitamin D and significantly higher level of alkaline phosphatase and parathormone in comparison with control cases.

Table 3 shows the echocardiographic parameters of cases in group 1 compared with group 2. LVEDD & LVESD were significantly higher while EF% and FS% were significantly lower in group 1 when compared with group 2. No statistically significant difference in IVSWT, LVPWT, I/L, LVM, LVMI and E/A in either group 1 or 2.

Table 4 shows the echocardiographic parameters of the studied patients with low calcium level compared with normal calcium level, cases with low calcium level had significantly higher LVEDD & LVESD and lower FS% & EF % compared with cases with low calcium level.

Table 5 shows the correlation between FS% and some biochemical and echocardiographic data among the studied cases. FS% correlated positively with serum calcium ($r = 0.489$, $P < 0.05$) and 25 (OH) vitamin D ($r = 0.762$, $P < 0.001$), and

Table 1: Demographic and anthropometric characteristics of the studied groups.

	Group 1 N= 100	Group 2 N=50	P value
Age (months)	9.4 \pm 1.2	7.2 \pm 1.6	NS
Gender Male / female	68/32	37/13	NS
Residence Urban /rural	23/77 (29.8%)	8/42 (19%)	NS
Weight (kg)	9.6 \pm 2.14	8.7 \pm 0.12	NS
Height/ length(cm)	74.6 \pm 13.2	72.5 \pm 11.3	NS
Head circumference(cm)	47.6 \pm 5.43	49.7 \pm 6.3	NS

Quantitative variables are expressed as mean \pm standard deviation, student t test were used. NS, non-significant result.

Table 2: Biochemical markers of the studied groups.

/	Group 1 N=100	Group 2 N=50	P value
Calcium (mg/dl)	7.1 \pm 0.6	9.4 \pm 0.8	P < 0.01
Phosphorus (mg/dl)	1.8 \pm 0.5	5.2 \pm 0.8	P < 0.001
Alkaline phosphatase (IU)	490 \pm 50.2	155 \pm 42.6	P < 0.001
Parthormone (pg/ml)	212 \pm 35.3	44 \pm 16.6	P < 0.001
25(OH) vitamin D (ng/ml)	5.2 \pm 1.3	23 \pm 1.8	P < 0.001

Quantitative variables are expressed as mean \pm standard deviation, student t test were used

Table 3: Echocardiographic characteristics of the studied groups.

Echo	Group 1 N=100	Group 2 N=50	P value
LVEDD (mm)	31.3 \pm 3.6	21.1 \pm 2.1	P < 0.01
LVESD (mm)	23.54 \pm 2.4	13.1 \pm 1.5	P < 0.01
EF (%)	57.4 \pm 9.2	69.5 \pm 8.6	P < 0.01
FS (%)	24.9 \pm 1.9	37.9 \pm 3.9	P < 0.01
IVSWT (mm)	3.5 \pm 0.4	4.1 \pm 0.6	NS
LVPWT (mm)	3.1 \pm 0.5	3.9 \pm 0.6	NS
I/L	1.2 \pm 0.08	1.05 \pm 0.01	NS
LVM (g)	30.77 \pm 4.2	32 \pm 3.9	NS
LVMI (g/m ²)	67.4 \pm 11.5	64.76 \pm 12.4	NS
E/A	1.1 \pm 0.05	1.3 \pm 0.09	NS

LVEDD ,Left ventricular end diastolic diameter ; LVESD, left ventricular end systolic diameter ;FS, fractional shortening; EF, ejection fraction; IVSWT, interventricular septal wall thickness; LVPWT left ventricular post wall thickness; I/L, interventricular post wall thickness / left ventricular post wall thickness; LVM, left ventricular mass; LVMI ,left ventricular mass index; E/A ratio ,E wave /A wave ratio. Quantitative variables are expressed as mean \pm standard deviation, student t test were used. .NS, non-significant result.

correlated negatively with Parthhormone ($r = -0.635, P < 0.001$), alkaline phosphatase ($r = -0.621, P < 0.001$) and LVEDD ($r = -0.814, P < 0.001$).

On follow up of the studied cases, 61 of them missed follow up and 39 cases appeared for follow up. Echocardiography was repeated for cases (N=39) who appeared for follow after 3 months of start of treatment for VDDR.

Table 6 shows the echocardiographic parameters before and after treatment. After treatment with vitamin D and calcium, the measurements of LVEDD & LVESD were significantly lower ($P < 0.01$ for both) in comparison to their values before treatment, while EF% & FS% were significantly higher ($P < 0.05$ for both) in comparison to their values before treatment. It was also observed that no significant difference in echocardiographic parameters after treatment compared with control group. This means improvement in echocardiographic parameters after treatment of VDDR with vitamin D and calcium.

Discussion

Rickets is commonly recognised disease in Egypt, the factors responsible for occurrence of rickets in Egypt are repeated poorly spaced pregnancies with lack of maternal vitamin D supplementation, the dusty atmosphere especially during winter and spring, lack of health and nutritional education, the habit of excessive wrapping of infants and keeping them indoors without exposure to sunlight, poor housing and faculty weaning [10].

Vitamin D has net effect of increasing serum levels of calcium and phosphate levels and achieves this by increasing intestinal calcium and phosphorus absorption. Vitamin D deficiency results in reduced serum calcium, which triggers secretion of parathyroid hormone (PTH) to release calcium and phosphorus from bone in an attempt to maintain normal serum calcium levels [11].

Table 4: Echocardiographic parameters of the studied patients with low calcium level compared with those with normal calcium level.ro

Cases	LVEDD (mm)	LVESD (mm)	FS %	EF %	I/L	E/A
Low Ca (N = 42)	34.2±5.1	25.9±2.1	24.20±1.77	56.56±8.7	1.1±2.7	1.2±0.76
Normal Ca (N = 58)	28.19±3.8	18.67±2.65	33.77±4.25	70.6±9.9	1.13±0.39	1.1±2.5
P value	P< 0.05	P< 0.05	P<0.01	P<0.01	NS	NS

Low calcium <8.8 mg/dl.⁹

LVEDD ,Left ventricular end diastolic diameter ; LVESD ,left ventricular end systolic diameter; FS, fractional shortening; EF, ejection fraction; I/L, interventricular post wall thickness / left ventricular post wall thickness; E/A ratio , E wave /A wave ratio

Quantitative variables are expressed as mean±standered deviation Mann-Whitney U-test was used;,NS, non significant result.

Table 5: Correlation between FS % and some biochemical and echocardiographic data.

	calcium	ALP	PTH	25 (OH)Vit D	LVEDD
FS%	$r = 0.489$ $P < 0.05$	$r = -0.621$ $P < 0.001$	$r = -0.635$ $P < 0.001$	$r = 0.762$ $P < 0.001$	$r = -0.814$ $P < 0.001$

FS %,Fractional shortening;ALP, alkaline phosphatase; PTH, Parathormone; 25 (OH)Vit D, 25(OH) vitamin D;LVEDD ,left ventricular end diastolic diameter

Table 6: Echocardiographic parameters before and after treatment of the studied cases.

	Before treatment N =39	After treatment N=39	Control N=50	P value		
				Before vs after	Before vs control	After vs control
LVEDD(mm)	30.6±3.33	20.56±2.2	21.1±2.1	P<0.01	P<0.01	NS
LVES (mm)	22.22±2.3	14.76±1.7	13.1±1.5	P<0.01	P<0.01	NS
EF (%)	62.18±8.33	66.01±9.79	69.5±8.6	P<0.05	P<0.05	NS
FS (%)	27.44±2.8	35.86±3.6	37.9±3.9	P<0.05	P<0.01	NS
IVSWT(cm)	3.2±0.5	3.6±0.85	4.1±0.6	NS	NS	NS
LVPWT(cm)	3.3±0.4	3.5±0.82	3.9±0.6	NS	NS	NS
I/L	1.03±0.05	1.07±0.07	1.05±0.01	NS	NS	NS
LVM(g)	33.54±4.8	31.65±3.4	32±3.9	NS	NS	NS
LVMi(g/m ²)	68.4±12.3	65.43±11.7	64.76±12.4	NS	NS	NS
E/A	1.15±0.05	1.23±0.07	1.3±0.09	NS	NS	NS

39 cases with VDDR appeared for follow up after treatment with vitamin D and calcium while 61 with VDDR missed follow up after discharge from hospital.

LVEDD ,Left ventricular end diastolic diameter ; LVESD, left ventricular end systolic diameter LVESD ;FS, fractional shortening; EF, ejection fraction; IVSWT, interventricular septal wall thickness; LVPWT left ventricular post wall thickness; I/L, interventricular post wall thickness / left ventricular post wall thickness; LVM, left ventricular mass; LVMi ,left ventricular mass index; E/A ratio, E wave /A wave ratio.

Quantitative variables are expressed as mean±standered deviation, student t test were used. .NS, non significant result

In the present study, serum calcium level was significantly lower in group 1 when compared with group 2. Hypocalcaemia is an important cause of reversible cardiomyopathy and lack of awareness of this etiology may lead to inappropriate therapy of cardiac failure with loop diuretics, leading to a worsening of hypocalcaemia and its possible acute life threatening manifestations (laryngeal spasm, prolonged QTc, ventricular arrhythmias, and refractory hypotension), by increasing renal excretion of calcium. Overt cardiac failure does not develop in most patients with hypocalcaemia. This is because of development of symptomatic neuromuscular irritability, causing the majority of hypocalcemic patients to seek early medical attention. Infants with hypocalcemia usually present with tetany or seizures early, thus rarity of hypocalcemic heart failure [12].

EF% and FS% are the most commonly used parameters in the clinical evaluation of systolic functions of the left ventricle [13]. This work shows, EF% and FS% significantly lower in group 1 in comparison with group 2. This indicated presence of systolic dysfunction and poor left ventricular contraction among cases with VDDR. Also, the LVEDD and LVESD were significantly higher in group 1 in comparison with group 2 (Table 3). This signify the presence of dilated left ventricle among studied VDDR cases. The combination of dilated left ventricle and poor contractility of left ventricle implying dilated cardiomyopathy among VDDR cases. In addition, the above mentioned echocardiographic parameters were significantly affected in cases with hypocalcemia when compared with cases with normal calcium level (Table 4). Available literature has case reports of hypocalcemia as the cause of cardiomyopathy in pediatric age group [14,15]. Maiya, et al. [16], reported 16 cases of cardiomyopathy in children associated with vitamin D deficiency leading to hypocalcaemia over a period of 6 years. On the other hand, adults with ventricular dysfunction, hypoparathyroidism was found to be the main reason for hypocalcemia [17-19].

In the studied group of patients, we did not find any statistically significant difference in LVM, LVMI, IVPWT, LVPWT and I/L ratio among cases in group 1 when compared with group 2 (Table 3), this indicated absence of hypertrophic cardiomyopathy among our studied cases with VDDR. Uysal et al. [9], had studied cardiac function in 27 infants with vitamin D deficiency rickets. They divided the patients into three groups according to their biochemical profile. In stage 1, hypocalcemia was the only significant biochemical abnormality. In stage 2, serum calcium returned to normal, but hypophosphatemia appeared because of secondary hyperparathyroidism. The stage 3 encompassed symptomatic rickets, worsening hypophosphatemia, and recurrence of hypocalcemia. They found that hypertrophic cardiomyopathy (I/L ratio >1.3) may develop in rickets, especially in the third stage of the disease, and this finding may return to normal following adequate treatment of rickets. The difference between the result of our study and Uysal et al., study could be attributed to difference in patient's numbers and different stages of enrolment of cases in both studies.

Also it was found that, 25 (OH) vitamin D was significantly lower in group 1 when compared with group 2. There is an accumulating evidence suggests that vitamin D plays a role in cardiovascular disease. Vitamin D deficiency has long been known to affect cardiac contractility, vascular tone, cardiac collagen content, and cardiac tissue maturation [20].

In the present study, serum phosphorus level was significantly lower in group 1 when compared with group 2; the effect of hypophosphatemia on heart was a matter of controversy in various studies. Verd et al. [21], reported normal ventricular performance in 11 children with X linked hypophosphatemic rickets, while some other studies reported myocardial dysfunction due to hypophosphatemia [22,23].

Another observation was that, FS% correlated positively with serum calcium and 25 (OH) vitamin D, and correlate negatively with plasma PTH, alkaline phosphatase and LVEDD (Table 5). Calcium is of critical importance to numerous biologic functions, including muscle contraction, cardiac automaticity, and neuronal conduction. Normal serum calcium limits are maintained in the body by the interplay of parathyroid hormone and vitamin D. Vitamin D deficiency prevent the efficient absorption of dietary calcium and phosphorus which lead to hypocalcemia and hypophosphatemia [24].

Lastly, 61 cases after discharge from hospital missed follow up, this can attributed to that near 70% of our studied cases came from rural area and villages. Cases who received treatment for rickets and appeared for follow up (N=39) showed improvement of echocardiographic parameters after treatment with vitamin D and calcium (Table 6). Echocardiographic abnormalities in patients with VDDR denote the severity of the disease and its serious outcome which requires urgent effective measures to overcome this serious disease. Vitamin D treatment can reverse these abnormalities to a great extent.

Conclusions

Children with VDDR have a significant impairment in LV systolic functions which improved with appropriate treatment.

Recommendations

- 1- Early treatment with vitamin D and calcium can reverse cardiac changes in patients with VDDR.
- 2- Serum calcium and vitamin D levels must be estimated in all children presenting with cardiomyopathy.
- 3- Pediatricians should be aware of the association of hypocalcemia with cardiac dysfunction and should keep it as a possible reversible cause of heart failure in children.
- 4- Supplementation of vitamin D to breast feed infant should be a routine practise to all paediatricians to prevent VDDR. Vitamin D is important not only for bone health but also for cardiac function.

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