ORIGINAL RESEARCH PAPER

Pediatrics

"A CROSS SECTIONAL, DESCRIPTIVE STUDY ON SYSTEMIC ILLNESSES AND CARDIAC FUNCTION ABNORMALITIES IN CHILDREN"

KEY WORDS: Systemic illnesses, endocrine, haematological, renal,cardiac parameters,echocardiography

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ABSTRACT

Background: There are wide number of diseases of almost every system in the body which can affect heart in a number of different ways including increasing demands on the heart ,ventricular dysfunction ,rhythm abnormalities ,valve abnormalities ,pulmonary pressures and lot more.Cardiac involvement in systemic diseases is usually silent or oligo-symptomatic and includes different pathophysiological mechanisms such as myocardial inflammation, infarction ,subendocardial vasculitis, valvular disease and different patterns of fibrosis.

Objective : To study association between systemic illnesses (hematological, endocrinal , renal) and cardiac function abnormalities as ventricular function, cardiac dimensions ,pulmonary artery
pressure and pericardial effusion, for early diagnosis and treatment to decrease morbidity and mortality in patient with systemic illness.

Design/Method: It was a cross sectional, descriptive study
The present study was conducted in the Department of Pediatrics, LLRM Medical College, Meerut, Uttar Pradesh over a period of 1 year (June 2019-June 2020)

Results: Cardiac findings in all three groups show ECG abnormalities and echocardiographic changes compared to general population. ECG abnormalities were prolonged PR interval and sinus tachycardia while echocardiographic changes mainly left ventricular(LV) dilatation and hypertrophy ,increased cardiac output ,ventricular dysfunction and pulmonary arterial hypertension(PAH),were noted in a significant proportion of patients.

Conclusion: Systemic illnesses affect cardiac parameters in various ways including prolonged PR interval,cardiac dilatation,chamber hypertrophy , high cardiac output, high cardiac index ,PAH and ventricular dysfunction.

INTRODUCTION

The treatment and management of people with non-cardiac diseases changes rapidly, forcing cardiologists to be up to date on everything that may affect the cardiovascular system. So cardiology evaluation (chest X-ray, ECG, Echocardi ography, cardiac MRI, cardiac catheterization, coronary arteriography, and myocardial biopsy) can identify unique characteristic features. Echocardiography is the crucial noninvasive tool for cardiac evaluation providing structural and functional abnormalities and can be repeated if needed. It may provide prognostic information describing the extent or progression of cardiac involvement.Sometimes echo may be the first clue to the underlying systemic illness. It is important to determine the conditions and parameters which can affect the cardiovascular system and quantify the risk factors so that timely intervention and appropriate measures could be taken at appropriate time.

Our is a prospective study and all consecutive patients, age group 6 months to 18 years, with systemic illness are included. Of the various systemic illnesses, haematological, endocrinal and renal disorders constitute major part and so included in this study.

I)Anemia : Anemia is a major public health problem and remains one of the most prevalent and enfeebling morbidity suffered by individuals in the developing world(1),the commonest being iron deficiency anemia. Other types of anemia are megaloblastic , thalassemia,pernicious and sickle cell anaemia .World Health Organization (WHO) global database on anemia estimated the prevalence of anemia worldwide at 25% with the prevalence being as high as 43% in the developing countries(2,3). In anemia oxygen delivery to tissues decreases and oxygen extraction is increased. This lead to decreased venous haemoglobin saturation(4).Several studies have also supported the association between anemia and left ventricular diastolic dysfunction(5-7).

In thalassemia,chronic tissue hypoxia causes bone marrow expansion and spleen enlargement(8).In the era of systematic transfusion therapy, myocardial iron overload is traditionally thought to be the main cause of thalassemia cardiomyopathy (9,10).Iron toxicity has been attributed to the production of free oxygen radicals which take place in the presence of free iron, which is the most toxic form of iron(11).

Sickle cell disease is characterized by recurrent episodes of ischemia-reperfusion injury to multiple vital organ systems and a chronic hemolytic anemia, both contributing to progressive organ dysfunction.Myocardial ischaemia (MI) is increasingly recognised as a feature of sickle cell anaemia in both children and adults These often result in acute and chronic ischaemic complications which may involve any organ or tissue causing vasoocclusive crisis(12).

Megaloblastic anaemia is not rare, but data are insufficient regarding its prevalence. The condition is more prevalent in countries where malnutrition is a significant problem.

II) Renal: Main cohort of children with renal disease in our study is of nephrotic syndrome(NS) .There is an increased incidence of heart disease in patients with chronic NS, which may be attributable to the malnutrition and activated inflammatory state accompanying the sustained proteinuria (13). In NS, massive proteinuria is accompanied by hypoproteinemia, protein wasting, and lean body mass reduction. Anorexia and impaired intestinal absorption from the oedematous gut are also contributory, inducing malnutrition(14) .All these factors ,malnutrition,inflammation ,fluid and electrolyte imbalance and hypertension , will have

effect on cardiac functioning .

III)Endocrine : In our study population hypothyroidism, Type-1 DM, Vitamin D deficiency were making the cohort of children and studied here in detail.

a)Diabetes Mellitus

There is a growing evidence that diabetes can lead to systolic and diastolic cardiac dysfunction without other obvious causes for cardiomyopathy. In pediatric age group association of cardiac function and diabetes is not well defined. Studies are going on to establish the correlation between the two. There were significant differences in the diastolic function of both ventricles as well as in the systolic function of the right ventricle of patients with type 1 diabetes mellitus(15)

b)Hypothyroidism

Hypothyroidism has known effects on multiple cardiovascular pathways, including adverse effects on systolic and diastolic function, endothelial function, and lipid levels, and study suggests that if someone has higher underlying cardiovascular risk, they may be more vulnerable to the effects of mild hypothyroidism(16).The cardiac features of hypothyroidism include normal or slow heart rates and cardiomegaly. The latter is usually caused by pericardial effusion,which is a common feature.Heart rate abnormalities and pericardial effusions resolve when substitution done(17).

c)Vitamin D Deficiency

Vitamin D (Vit D) deficiency is highy prevalent and has been shown to be associated with cardiovascular diseases, including coronary artery disease, LV hypertrophy and systolic heart failure(18-21). Since diastolic dysfunction is an early manifestation of LV hypertrophy and ventricular dysfunction(22,23) ,it may reflect the effects of Vit D deficiency on the cardiovascular system. A study by Tomar et al(24) has demonstrated low serum calcium as the sole reason for severe left ventricular dysfunction in infants and in majority of cases Vit D deficiency was the reason for hypocalcemia.These patients responded to calcium and vitamin D supplementation promptly with normalization of LV function within few months of treatment.

MATERIALS AND METHODS:

Setting : This study was carried out in department of pediatrics , L.L.R.M. Medical College and associated S.V.B.P hospital,Meerut.

INCLUSION CRITERIA:

All consecutive children age group between 6 months to 18 yrs ,enrolled in department of paediatrics LLRM medical college,Meerut with specified systemic illnesses-

- Hematological (iron deficiency anemia, megaloblastic anemia, thalassemia)
- Renal disorders (nephrotic syndrome)
- Endocrinological (thyroid, diabetes mellitus, vitamin D deficiency)

EXCLUSION CRITERIA

- Neonates and infants below 6 months
- Age >18yrs
- Known cardiac structural defect
- Hemodyanamicaly unstable patient

Design:

This study was designed as cross sectional,descriptive study.

Ethical approval:

The study was approved by the Institutional Ethical Committee (IEC)

Consent:

Informed,written consent taken from one of the parent.

STATISTICAL ANALYSIS

Analysis of variance was applied in our data. P value of less than 0.05 was considered significant. Software used was stata 14.0 for analysis of data and R3.4.4 for graphs

METHODOLOGY

After taking proper written and oral consent, proper history was taken and routine blood investigations including complete blood count,general blood picture , renal and liver function test ,blood sugar and serum elctrolytes were sent.Specific investigations ,serum vitamin B12, serum vitamin D3, FT4, TSH, serum ferritin, HbA1c levels, were done as indicated. Accordingly, based upon laboratory investigations patient were grouped and then ECG and echocardiography was done in all the patients and parameters were studied.Echocardiographic parameters were compared with the reference age specific values(25)

Echocardiography was done in Super-specialty block, LLRM Medical college by GE Healthcare Vivid™ T8 machine with the use of broad band transducers (3Sc,6S).Standard views of echocardiography , subcostal(coronal and sagittal),apical ,parasternal long axis and short axis, high parasternal and suprasternal views ,were used for detailed definition .

Modes of echocardiography:

- Two-dimensional echocardiography
- M-Mode echocardiography
- Doppler echocardiography(Pulse wave and Continuous wave Doppler)
- Color Doppler mapping
- Tissue Doppler(TDI)

Defintions:

Cardiac function: Both systolic and diastolic functions are responsible for maintaining adequate cardiac output and should be assessed.

- **Systolic dysfunction** is defined in form of ejection fraction i.e. percentage of blood volume ejected in systole. Normal value for ejection fraction(EF) is more than 55%. LV dysfunction can be mild (EF 40-49%), moderate (EF 30-39%) and severe with EF less than 30%.(26)
- **Diastolic dysfunction** The ratio of E to E velocity (E/E) was computed as a surrogate of left ventricular (LV) filling pressure [10]. Diastolic dysfunction was graded as follows: grade 0 (no diastolic dysfunction), grade 1 (impaired relaxation) E/E ≤ 8, grade 2 (pseudonormal) E/E 9–12, and grade 3 (restrictive grade) E/E ≥ 13 (27).

PAH: The echocardiographic probability of PH was derived using the combination of tricuspid regurgitant(TR) velocity, early diastolic pulmonary regurgitant velocity, right ventricular size, interventricular septal motion ,and pattern of systolic flow velocity of pulmonary valve (28-31). TR velocity above 2.8 cm/sec was taken as elevated systolic right ventricular/PA pressure in absence of pulmonary stenosis.

Cardiac output: Stroke volume (SV) was calculated with the use of pulse wave Doppler across across left ventricular outflow tract (LVOT) and echo machine gives velocity time integral (VTI).

Formula to calculate stroke volume: LVOT area (r^2) X VTI
CO = Heart rate X Stroke volume

OBSERVATIONS AND RESULTS

Total patients enrolled in study were 190 and categorized into one of the three groups of haematological, endocrinal and renal(Table 1).

Anthropometry : Majority of patients of all 3 groups had BMI below18.5, IDA 33 (94.2%) patients, 9(90%) patients of MA, 53

(96.3%) patients of thalassemia, 14 (93.3%) patients of DM, 10 (83.3%) of hypothyroidism,32(96.9%) patients of Rickets and 18(60%) patients of nephrotic syndrome were underweight (Figure 1).

Group I (Hematological group):

ECG: Prolonged PR interval was found in 13(37.1%) IDA patients,1(10%) of MA patients and 14(25.4%) thalassemia patients(Figure 2). P wave axis and duration,QRS axis and duration and QTc interval were normal in all.None of the patient had arrhythmia .

Echocardiography:

- LVIDd Z-score + 2 or above was found in 2(5.7%) IDA patients.,1(10%) MA patiens and 1(1.8%) thalassemia patients. LVIDs Z-score +2 or above was found in 4(11.4%) IDA patients,1(10%) MA patients and 9(16.3%) pts of thalassemia .IVSd Z-score + 2 or above was found in 10(28.5%) IDA patients,2(20%) MA pts and 8(14.5%) thalassemia pts. IVSs Z-score +2 or above was found in 9(25%) IDA, 3(30%)MA and 2(3.63%) patients of Thalassemia. LVPWd Z-score +2 or above was found 14(40%) IDA,3(30%) MA and 11(20%) thalassemia patients. LVPWs Z-score +2 or above was found in 1(2.8%) IDA patients. LA Z-score value of + 2 or above found in 2(5.7%) IDA patients .So among hematological patients,cardiac dilatation and ventricular hyperytrophy was seen in significant population(figure 3).
- LV dysfunction (EF<50%) was found in 2(5.7%) IDA and 2(20%)MA patients while none of the TM patient had systolic ventricular dysfunction.
- Increase CO was found in 8(8%) patients and increase CI was found in 20(20%) in group I . High PA systolic pressure was found in 5(5.2%).In all 5 children,PA pressures were mildly elevated,none had modettae or severe PAH.

Group II (Endocrinal Group):

ECG: Prolonged PR interval was found in 6.66% DM patients and 27.2% patients with Vit D deficiency(Figure 2). QRS duration and axis and QTc interval were within normal range and none of the children had arrhythmia.

Echocardiography:

- LVIDd Z-score values of +2 or more was found in 1(6.6%) type 1 DM,2(6%) vit D defeceincy patients, LVIDs values of +2 or more was found in 1(8.3%) hypothyroidism patients,4(12%) of children with vit D defeceincy , IVSd Zscore values of + 2 or more was found in 2(13.3%) DM patients ,8(24.2%) vit D defeciency,and 2(16.6%) hypothyroidism patients . IVSs Z-Score values of +2 or more was found in 1(6.6%) DM patients . LVPWd Z-score values of +2 or high was found in 1(8.3%) hypothyroidism ,2(13.3%) DM , 12(36.3%) vit D deficiency patients . LA Z-score values of + 2 or above was found in 4(12.1%) with vit D defeceincy while it was within normal limit with DM and hypothyroidism .

So significant number of endocrinal patients have cardiac dilatation and ventricular hypertrophy(figure 4)

- High CO was found in 5(8.3%) , increase CI in 10 (16.6%) while 2 (2.1%) children had mild PAH in group II .

Group III (NS patients):

ECG: All children were in sinus rhythm with normal intervals and axis .

Echocardiography:

- Z score value + 2 or above was found for LVIDs in 1(3.3%) , IVSd in 2(6.66%),IVSs in 3(10%), and LVPWd in 1(3.3%) children with NS (figure 4).
- In our study,EF<50% was found in 2(6.6%) while one patient (3.6%) had mild PAH with NS .
- Increase CI was found in 2(8.3%) patients with NS.
- Our observation showed ECG abnormalities and echocardiographic changes in all three groups in significant population(figure 2,3 and 4, table 2).

Table 3 Showed our observation of tissue Doppler imaging (TDI) in all 3 groups and we found that there was no statistical difference in TDI values and TDI values in our study are in accordance to reference range.

Diastolic Dysfunction (DD) (calculated by TDI value of E/E') of Grade 1 was found in 9(25%) IDA patients,1(10%) of MA patients, 22(40%) of Thalassemia patients,4(26.6%) of DM patients,5(41.6%) of Hypothyroidism patients ,7(21.2%) of Vitamin D deficiency patients and 7(23.3%) of NS patients DD of grade 3 was found in 3(3%) patients of group I . 1(1.6%) patients of group II and none of NS patient had grade III DD.

DISCUSSION-

The present study focused to find out the incidence of cardiac function abnormalities in various systemic illnesses ie, hematological disorder ,renal disorder and endocrinal disorders.Very few studies are available on pediatric population and their cardiac evaluation **.Hussein et al.**(32) conducted a transthoracic Doppler echocardiographic study in 200 patients to evaluate the relationship between anemia and diastolic dysfunction. Our study showed diastolic dysfunction in 9(25%) IDA patients,1(10%) of MA patients, 22(40%) of Thalassemia patients. These results are in accordance to our study.

Further our study adds that prolonged PR interval alongwith increase in Z scores of M mode of echocardiography were present in significant patients with anemia (group I).

Uysal et. al.(33) in their study showed abnormal ECG findings in infants with rickets before treatment and documented that these changes resolved following treatment. Echocardiographic studies revealed left ventricular dysfunction in the pre-treatment stage.Very few studies were done for PA pressures,CO,CI. Our study showed cardiac chamber dilatation ,ventricular hypertrophy , increase PA pressures,increase CO and CI in patients with vitamine D deficiency. **Varma et al**(34) showed that hypothyroidism, both subclinical and overt is associated with cardiovascular alteration both structural and functional. IVS and LVPW thickness are markedly affected, as well as there is impairment of left ventricular function more in diastole.Our study also document cardiac dilatation and hypertrophy. Present study further adds that grade I Diastolic dysfunction was present in 5 (41.6%) of Hypothyroidism patients.

Z-d Du et al (35)showed abnormal ECG findings and echocardiographic parametes in children of NS .These results are in concordance with our study as our study shows high PA pressures in 3.6% patients , diastolic dysfunction in 23.3% patients along with increase Z-scores of M-mode echocardiography.

So all patients of anemia, endocrinal and renal group needs detail cardiac evaluation and annual echocardiography so that early diagnosis could be made and if needed, intervention can be taken .These patients need to be followed up regularly with annual echocardiography as chronicity of disease can adversely affect the heart.

What was previously known?

Very few studies were done which shows increase cardiac dimensions and increase CO in patients of anemia, thalassemia and rickets

What this study adds?

Prolonged PR interval,mild PAH ,high EF,increase cardiac index,increase Z-score values of M-mode echocardiography seen in various systemic illnesses.

Limitation of study: Beginning of Corona pandemic during study period has affected our study leading to :

1. Smaller number in each group
2. We do not have our control group . We could not call normal children to hospital for cardiac evaluation .We compared our ECG and echo findings with the normative data available online(25,26,27,36) .
3. Follow up cardiac evaluation could not be done .

Future plan:

1. Cardiac evaluation of the enrolled children on annual basis
2. Study cardiac parameters (ECG and Echo) in children without systemic disease to have a comparative data

CONCLUSION-

Systemic illnesses affect cardiac parameters in various ways including prolonged PR interval, cardiac dilatation and hypertrophy ,high cardiac output, high cardiac index ,increase PA pressures , and ventricular dysfunction .As these illnesses have chronic effect on heart so patient need to be followed up further.With early detection of cardiac dysfunction ,early institution of cardiac medication will delay or prevent further cardiac function deterioration.

Table 1: Total number children enrolled in different groups with age and sex distribution

Group	Disease	Total number	Male/ Female	Age		
				<1 year	1 to 5 year	> 5 year
I	Hematolgical	100	66/34	22	39	39
	a. IDA	35	20/15	8	20	7
	b. MA	10	3/7	3	4	3
	c. Thalassemia	55	43/12	11	15	29
II	Endocrine	60	30/30	15	19	26
	a. DM	15	7/8	0	1	14
	b. Hypothyroidism	12	6/6	0	4	8
	c. Vit D def	33	17/16	15	14	4
III	Renal:NS	30	14/16	0	17	13

Table 2- Distribution of participants according to systemic diseases and their Echo findings (M mode):

Echo Findings (M mode)	Systematic Diseases			
	Endo (n=60)	Hemat (n=100)	Renal (n=30)	P-value
RVIDd	-1.78±1.04	-1.49±0.97	-1.76±1.01	0.161
LVIDd	0.05±1.47	0.26±1.26	0.50±1.05	0.282
LVIDs	0.59±1.07	1.66±10.13	-2.19±10.9	0.098
IVSd	1.12±1.51	1.15±1.28	-0.09±1.57	**<0.001**
IVSs	0.66±1.19	0.64±1.28	0.60±1.14	0.970
LVPWd	1.30±0.95	1.38±1.11	1.20±0.66	0.688
LVPWs	-0.74±0.96	-0.55±1.07	-0.14±1.06	**0.001**
LA	0.21±1.30	0.84±1.59	0.17±1.18	**0.011**

Table 3- Distribution of participants according to systemic diseases and their Echo findings (TDI mode):

Echo Findings (TDI mode)	Systemic Diseases			
	Endo (n=60)	Hemat (n=100)	Renal (n=30)	P-value
Mitral medial				
S	7.75±1.66	8.52±2.26	8.50±2.39	0.064
E`	10.12±2.32	11.05±2.43	10.75±2.15	0.054
A`	6.17±1.61	6.56±1.91	7.20±2.09	0.053
Mitral lateral				
S	7.63±1.69	8.42±1.89	8.43±2.14	**0.027**
E`	10.94±3.16	12.24±3.37	12.21±3.27	**0.044**
A`	6.18±1.98	6.46±1.83	7.37±2.87	**0.038**
RV free wall				
S wave	12.48±2.67	12.99±2.69	13.05±2.78	0.459

TDI: tissue Doppler imaging, RV: right ventricle

Legends:

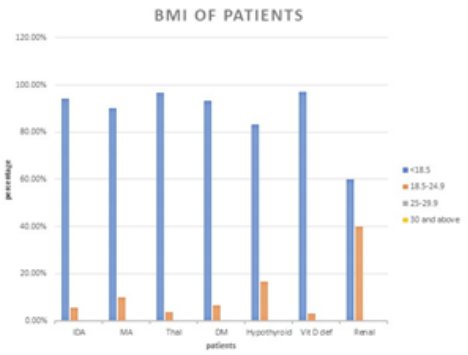

Figure 1

Figure 1: Bar chart showing BMI of patients in different groups

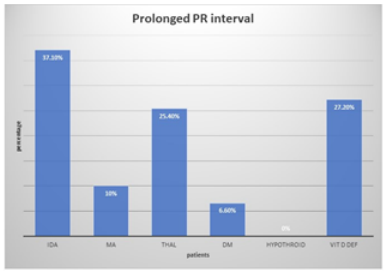

Figure 2

Figure 2: Bar chart showing PR interval in group I and II

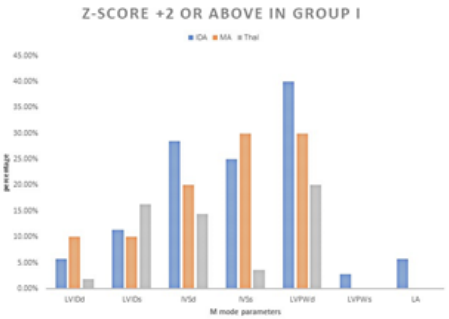

Figure 3

Figure 3: Bar chart showing cardiac dimensions Z-Score values of +2 or above on M-mode echocardiography in group I

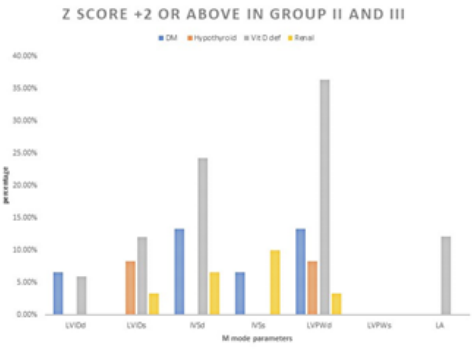

Figure 4

Figure 4: Bar chart showing cardiac dimensions Z-Score values of +2 or above on M-mode echocardiography in group II and III patients

Abbreviations :

IDA	Iron Deficienncy Anemia
MA	Megaloblastic Anemia
TM	Thalassemia Major
DM	Diabetes Mellitus
NS	Nephrotic Syndrome
LVID	left ventricular internal diameter
IVS	interventricular septum
PW	posterior wall
RV	right ventricle
EF	ejection fraction
CO	cardiac output
CI	cardiac index
ECG	electrocardiograpm

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