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"A PROSPECTIVE STUDY OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AND PULMONARY HYPERTENSION IN PATIENTS OF SICKLE CELL ANAEMIA IN RIMS RAIPUR "

Dr Ramgopal Ghritlahare	Associate Professor, Department of Medicine,RIMS, Raipur, Chhattisgarh, India-492001
Dr.Brajendra Kumar	Professor, Department Medicine, RIMS, Raipur, Chhattisgarh, India-492001
Dr.J.P.Sachdeva	Assistent Professor, Department of Medicine,RIMS, Raipur, Chhattisgarh, India-492001

ABSTRACT

Sickle cell disorder (SCD) was the first diagnosed disease that was linked to the hemoglobin protein and genetically characterized. It is an autosomal recessive disorder that occurs throughout the world. The distribution of SCD often coincides with that of falciparum malaria parasites, therefore making it common among people from sub-Saharan Africa, Mediterranean countries, Southern India and their descendants (African Americans) (**Weatherall et al, 2005**).The aim of our study was to assess prevalence of Pulmonary hypertension and Left ventricular diastolic dysfunction by using 2D Echocardiography in the patients of sickle cell anemia.This study was conducted in the Department of Medicine, RIMS, Raipur (C.G.) among the patients presenting in O.P.D. and admitted in medicine ward from Dec. 2014 to Sep. 2016.A total of 100 patients were taken fulfilling the inclusion criteria for the study. Detailed clinical history was recorded and allpatientsunderwent complete clinical examination.Hb electrophoresis and 2D Echocardiography of all patients were done.In our study out of 100 patients, 34 patients (34%) were male while 66 patients (66%) were female.70 subjects were having sickle cell trait out of which 18 patients were male and 52 were female, whereas 30 subjects were having sickle cell disease out of which 15 patients were male and 15 were female. Mean Hb level was 8.41 ± 1.74 gm%. In our study population maximum Hb was 12 gm% whereas minimum Hb was 4 gm%.Diastolic dysfunction was present in 50% of the total cases (100) among them 45.45% were males, 52.23% were females. Diastolic dysfunction was almost equally prevalent among female compared to male (p=0.51).Mean age of women with diastolic dysfunction was 29.37 ± 9.89 yrs, whereas mean age of men with diastolic dysfunction was 29.82 ± 10.24 yrs. Statistically there was no association was found between age and LVDD prevalence(p=0.99).In our study we found prevalence of LVDD in studied genotypes i.e. AS and SS to be almost similar (P = 0.62, non-significant). Our study showed that diastolic dysfunction is more closely associated with moderate (Hb level 7-10 gm%) and severe anemia (Hb level 4-7gm%) than mild anemia (Hb level >10%). Statistically it was found to be significant (p=0.006).Mean Hb level of patients with diastolic dysfunction was 7.88 ± 1.81 gm%, whereas mean Hb level of patients without diastolic dysfunction was 8.94 ±1.49 gm% (P<0.01, significant).Pulmonary Hypertension (PH) was present in 24 cases (24%) of the study population, among them 5 were males and 19 were females. There was no significant difference of prevalence of PH between both genders. (p=0.14).Out of 100 patients 12 patients (12%) had both LVDD and PH.The findings in our study indicate that in patients of sickle cell anemia, left ventricular diastolic function is impaired much before development of systolic dysfunction. Lower Hb levels in patients of sickle cell anemia is associated with cardiopulmonary complications. No significant correlation was found in respect to prevalence of PH and LVDD with age or gender.More so presence of both PH and LVDD significantly contributes to a higher mortality in patients of sickle cell anemia. Therefore by early detection we can start early treatment and can retard the progression of these cardiopulmonary abnormalities and its future consequences. Doppler Echocardiography is a simple, non-invasive, easily available technique that identifies sickle cell subjects who have asymptomatic pulmonary hypertension and/or left ventricular diastolic dysfunction much before abnormalities detected on ECG or by clinical examination. Therefore echocardiography becomes an indispensable tool for assessment of cardiac function in SCD patients.**The term sickle cell disorder (SCD) is used in a generic sense to refer to all the clinically severe sickling syndromes. The genetic abnormality involves the substitution of thymine with adenine in the sixth codon of beta gene (GTG ->GAG). So glutamic acid is replaced by valine and Hb S is produced, which upon deoxygenation undergoes polymerization leading to expression of sickling syndromes.**

KEYWORDS : PULMONARY HYPERTENSION, LEFT VENTRICULAR DIASTOLIC DYSFUNCTION, SICKLE CELL ANAEMIA.

INTRODUCTION:-

Sickle cell disorder (SCD) was the first diagnosed disease that was linked to the hemoglobin protein and genetically characterized. It is an autosomal recessive disorder that occurs throughout the world. The distribution of SCD often coincides with that of falciparum malaria parasites, therefore making it common among people from sub-Saharan Africa, Mediterranean countries, Southern India and their descendants (African Americans) (**Weatherall et al, 2005**).It is estimated that around 200000 to 300000 people are born every year with SCD worldwide (**Siddiqui AK et al 2003**). Prevalence of Sickle cell disorder is seen in decreasing order in blacks of Tropical African ancestry, Mediterranean basin, Saudi Arabia, Kuwait, Iran and India (**Kar BC 1991**). DNA polymorphism studies have shown that three independent mutations have given birth to βs gene responsible for SCD in blacks and Mediterranean, whereas a new fourth mutation resulted to βs gene in Saudi & Indian people (**Seargeant GR 1994**). The sickle cell gene was first described in India in a tribal population in the south (**Brittenham G et al 1977**). It is widespread in the state of Orissa and spreads throughout Hindu society, being more common in scheduled castes and upper castes than in tribal groups (**Kar BC 1991**). As per **Das MK et al** (**1995**) wide range of variation (0.00-0.14) in the frequencies of the HbS allele has been observed among 16 ethnic groups of central India. **The term sickle cell disorder (SCD) is used in a generic sense to refer to all the clinically severe sickling syndromes. The genetic abnormality involves the substitution of thymine with adenine in the sixth codon of beta gene (GTG ->GAG). So glutamic acid is replaced by valine and Hb S is produced, which upon deoxygenation undergoes polymerization leading to expression of sickling syndromes.**

Material And Methods

The study was conducted in the Department of Medicine, RIMS, Raipur (C.G.) among the patients presenting in O.P.D. and admitted in medicine ward from Dec. 2014 to Sep. 2016.A total of 100 patients were included fulfilling the inclusion criteria for the study. Patient's informed consent was taken. Detailed clinical history was recorded including age, sex, presenting complaints, past, personal and family history. All patients underwent complete clinical examination, laboratory investigation including Hb Electrophoresis and Doppler

Echocardiography of patients were done. Transthoracic echocardiography was performed with the use of the Mindray M7 echocardiography machine. Cardiac measurements were performed according to American Society of Echocardiography guidelines. The LV ejection fraction was assessed using M-Mode with help of "Teichholz"equations.Tricuspid regurgitation jet velocity(TRV) was assessed and pulmonary hypertension was prospectively defined as a peak TR jet velocity of at least 2.5m/s.Diastolic function was assessed in all patients using pulse doppler peak E and A velocities, E/A ratio, and deceleration time. Inclusion Criteria for study group:1. Patients with HbSS or Hb AS blood type on Hb electrophoresis.2. Age group between 16 years to 70 years. Exclusion Criteria for study group:1.Sickle cell anemia with any preexisting cardiac including valvular heart disease.2. Patients with primary and secondary pulmonary artery hypertension.3. Patients with preexisting hypertension, diabetes, chronic kidney disease and LVDD.

RESULTS

This study entitled "Study of Pulmonary Hypertension and Left ventricular diastolic dysfunction in patients of Sickle Cell Anaemia" was conducted in Department of Medicine, RIMS, Raipur on 50 patients of sickle cell anemia. In our study out of 100 patients, 34 patients (34%) were male while 66 patients (66%) were female. Most of the subjects were between 15 – 24 years of age and comprised 42% of sample size, subjects above 55 years comprised 6 % of sample size. 70 subjects were having sickle cell trait (AS) genotype out of which 18 patients were male and 52 were female, whereas 30 subjects were having sickle cell disease (SS) genotype out of which 15 patients were male and 15 were female. Our study is different from various studies available in literature who have only included sickle cell disease patients and hence not much data was available with respect to cardiopulmonary abnormalities in sickle cell trait patients. Out of 100 cases, 16 cases (16%) had Hemoglobin (Hb) level between 4 to 7 gm%, whereas 74 cases (74%) had Hb level between 7 to 10 gm%. 10 cases (10%) had Hb level between 10 to 13 gm%. Mean Hb level was 8.41 ± 1.74 gm%. In this study population Maximum value of Hb was 12 gm% whereas minimum value was 4 gm%. Diastolic dysfunction was present in 50 (50%) of the total cases among them 33 were males, 67 were females. Diastolic dysfunction was almost equally prevalent among female compared to male (p=0.51).Mean age of women with diastolic dysfunction was 29.37 ± 9.89 yrs, whereas mean age of men with diastolic dysfunction was 29.82 ± 10.24 yrs. Diastolic dysfunction was prevalent in 50% of patients in age group of 15 -24 years and was prevalent in 50 % of patients with age group more than 55 years. Out the 42 cases of age between 15-24 yrs , diastolic dysfunction was present in 21 (50% cases of 42) case and absent in 21 (50% cases of 42) cases. Statistically there was no association was found between age and LVDD prevalence(p=0.99).LVDD was present in 34 (48.57%) cases out of 70 cases of sickle cell trait whereas out of 30 patients of Sickle cell disease LVDD was present in 16 (53.33%) cases. in our study we found prevalence of LVDD in different genotype is almost similar. (P = 0.62, non-significant). Out of 16 cases having Hb level between 4-7 gm%, LVDD present in 13 cases (81.25 %), whereas in 74 patients with Hb level between 7-10%, LVDD was present in 33 cases (44.59%). Among 10 patients of Hb level 10-13 gm% group, 4 cases (40%) had LVDD. Our study showed that diastolic dysfunction is more closely associated with lower Hb level. Statistically it was found to be significant (p=0.006). Mean Hb level of patients with diastolic dysfunction was 7.88 ± 1.81 gm%, whereas mean Hb level of patients without diastolic dysfunction was 28.94 ± 1.49 gm%. (P<0.01, significant). Pulmonary Hypertension (PH) was present in 24 (24%) cases out of the total 100 cases, among them 5 were males and 19 were females. There was no significant difference of prevalence of PH between both genders. (p=0.14).Out of 100 patients 12 patients (12%) had both LVDD and PH.Mean age of women with PH was 29.37 ± 9.89 yrs. Mean age of men with PH was 29.82 ± 10.24 yrs. PH was most prevalent among age group of 55-65 yrs which had PH in 50% of its population. There is no linear relationship between subjects age and prevalence of PH. Statistically it was found to be non significant.(p=0.91). PH was present in 16 (22.85%) cases out of 70 cases of sickle cell trait whereas out of 30 patients of Sickle cell disease LVDD was present in 8 (26.66%) cases . There was no significant difference in prevalence of PH found between both genotype. (p=0.68).All PH cases had Hb level < 10gm%. This study suggested that PH in sickle cell anemia is more prevalent in patient presented with moderate to severe anemia then patient having mild anemia or near normal Hb level. Though statistically it was found to be insignificant. (p=0.59).In this study 24 patients had TR velocity ≥ 2.5 m/sec, which represent Doppler defined PH in study population. Mean TRV in patients of group <2.5 m/sec (i.e. patient. with no PH) was 0.76 ± 0.98 whereas Mean TRV in patients of group ≥ 2.5 m/sec (i.e. patient. with PH) was 2.88 ± 0.34. This findings was statistically significant with P value <0.001.Out of 100 patients 44 patients had E/A <1, whereas 56 patients (56%) had E/A ≥ 1. Mean value of E/A = 0.9 ± 0.48 in patients with E/A <1, whereas mean value of E/A =1.26 ± 0.34 in patients with E/A ≥ 1. This findings were statistically significant (p <0.001).Out of 100 cases 26 cases had DclrT <140 msec, where as 64 cases had DclrT between 140-220 msec.4 patients out of 100 had Dclr T >220 msec. Mean DclrT value in our population was 166.45 ± 38.82 msec with 312 msec as minimum value and 520 msec as maximum value.In our study mean LVEF of study population was 66.80±8.24 , while in patients had PH mean LVEF was 66.50±8.06 and in patients with LVDD mean LVEF was 66.46±8.93. Only 9 (9%) cases had LVEF < 55%, in which 5 patients had LVDD and 3 patients found to had PH. So we can conclude that systolic function is preserved in our patients. (p= 0.68 for LVDD patients and p=0.83 for PH patients, both were non significant.)

Discussion:-

Sickle cell disease (SCD) is characterized by recurrent episodes of ischemia-reperfusion injury multiple vital organ and chronic hemolytic anemia both contributing to progressive organ dysfunction. As a result there is development of progressive proliferative systemic vasculopathy, pulmonary hypertension (PH) and left ventricular diastolic dysfunction (LVDD).Chronic anemia in SCD results in cardiac chamber dilatation and compensatory increase in LV mass which is accompanied by left ventricular diastolic dysfunction. Pulmonary hypertension and left ventricular diastolic dysfunction are independent risk factor for mortality in SCD. **(Sachdev V, Machado R F et al.)**Present study was done in patient of sickle cell anemia to assess the prevalence of pulmonary hypertension and left ventricular diastolic dysfunction with the help of 2D echocardiography to recognize and treat these high risk patient, as pulmonary hypertension and left ventricular diastolic dysfunction are strong and independent predictor of mortality.Of the 100 patients included in the study, 70 (70%) were sickle cell trait (AS) and 30 (30%) were sickle cell disease (SS).There were 18 males (18%) and 52 females (52%) of sickle cell trait and there were 15 males (15%) and 15 females (15%) of sickle cell disease.The ratio of AS to SS was 2.3:1.Majority of patients in the study were of sickle cell trait then sickle cell disease. **In contrast to our study Pathak J et al, who studied 50 patients had 36 (72%) sickle cell disease and 14 (28%) sickle cell trait.**

CONCLUSION

Our study indicates that myocardial damage in patients with sickle cell patients left ventricular diastolic function before systolic function. Cardiopulmonary complication is associatated with Hb level. There is no significant correlation found in prevalence of PH and LVDD with age or gender. Improved medical care in SCD has seen a rising number of chronic complications merging with time, particularly PH, which has

been linked to high mortality rate of up to 50%. Doppler Echo is simple, non invasive, reproducible, safe and easily available. It identifies large percentage of sickle cell subjects who have asympatientomatic pulmonary hypertension and/or left ventricular diastolic dysfunction before abnormalities are detected with ECG or by clinical examination. Therefore by early detection we can start early treatment and can retard the progression of those cardiopulmonary abnormalities and its future consequences. Furthermore, increased life expectancy in SCD patients as a result of improved medical management demands clarification of the type of cardiac remodelling involved to help identify patients likely to develop cardiac dysfunction. The data presented in this thesis appears promising. However, longer-term follow up studies in patients with increased cardiac volumes are essential to accurately rule out detrimental cardiovascular events.

REFERENCES

[1]. Rees D.C., Williams, T.N. & Gladwin, M.T. (2010) Sickle-cell disease. Lancet, 376, 2018–2031.[2].Lindsay, Jr, J., Meshel, J.C. & Patterson, R.H. (1974) The cardiovascular manifestations of sickle cell disease. Archives of Internal medicine, 133, 643-651.
[3]. Hebbel, R.P. (1997) Adhesive interactions of sickleerythrocytes with endothelium. The Journal of Clinical Investigation, 100, S83-S86.
[4]. Butrous, G., Ghofrani, H.A., and Grimminger, F. (2008). Pulmonary vascular disease in the developing world. Circulation 118, 1758-766.Caldas, M.C., Meira, Z.A. & Barbosa, M.M. (2008) Evaluation of 107 patients with sickle cell anemia through tissue Doppler and myocardial performance index. Journal of the American Society of Echocardiography, 21, 1163 -1167.
[5]. Reiter CD, Wang X, Tanus -Santos JE, Hogg N, Cannon RO, 3rd, Schechter AN, et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. Nat Med.2002;8:1383 -9
[6]. Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease.N Engl J Med.2008;359:2254-2265.
[7]. Balfour I.C., Covitz W., Davis H., Rao, P.S., Strong, W.B. & Alpert, B.S. (1984) Cardiac size and function in children with sickle cell anemia. American Heart Journal, 108, 345-350.
[8]. SachdevV., Machado, R.F., Shizukuda, Y., Rao, Y.N., Sidenko, S., Ernst, I., St Peter, M., Coles, W.A., Rosing, D.R., Blackwelder, W.C., Castro, O., Kato, G.J. & Gladwin, M.T. (2007) Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. Journal of the American College of Cardiology, 49, 472-479.
[9]. Pathak J, Vadivelan M, Mathew C.Evaluation of Cardiac Status of Sickle Cell disease Patients by 2 D Echocardiography with special reference to Pulmonary Hypertension. Indian Journal of Clinical Practice 2013;Vol.23(11): 694-697.
[10]. Zilberman MV, Young EM, Du W, et al. Pulmonary hypertension in pediatric patients with sickle cell disease: a retrospective study.Blood. 2004; 104:23b.