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RESEARCH ARTICLE

RENAL DOPPLER-A SCREENING TOOL OF CHOICE FOR SICKLE NEPHROPATHY

***Bhushita Lakhkar**

Assistant Professor, India

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ABSTRACT

Background: Sickle cell anemia induces sickling of red cells due to polymerisation of sickle haemoglobin. Renal medulla is hypoxic and hypertonic and hence RBC are more prone to sickling. Some authors observed that changes in renal doppler indices {resistive index (RI), Pulsatility index (PI)} occur earlier than rise in biochemical parameters, hence this might be a better screening tool. **Aims**: correlation of renaldopplerindices in sickle cell anemia patients with biochemically normal, lower than normal and high renal function parameters. **Methods**: 108 Sickle cell patients between 6 month to 50 yrs, were subjected to Complete haemogram, renal function tests, ultrasonography of kidneys, followed by renal doppler study. Results were analyzed using SPSS software 23.Analysis **Result**: Of 108 patients,67.5% belonged to homozygous and 32.4% belonged to heterozygous group. Maximum patients belonged to an age group of 10-19 yrs and 1-9 yrs. RI and PI of the renal vessels were studied. Earliest changes were detected in interlobar artery. 43.6% patients of SS type and 27.2% of AS type had abnormal doppler changes. Increase in RI and PI was seen maximum in age group of 5-14 yrs (66 and 56% respectively) and 15-19 yrs. On comparission of renal indices with biochemical parameter, mean RI and PI were higher in children with low and high biochemical parameters as compared to children with normal biochemical parameters indicating more severe vascular changes. **Conclusion**: Study of renal indices in sickle cell patients is very useful in detecting early renal damage.

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INTRODUCTION

Sickle cell anemia is a hemo-globinopathy due to point mutation inβ globin gene at 6th position 11th chromosome, where glutamine is replaced by valine in the β globin chain of hemoglobin molecule. In this condition hypoxia induces sickling of red cells due to polymerisation of sickle haemoglobin (HbS), and this being a repeated phenomenon causes repeated trauma and reduces the elasticity of RBCs by damaging the membrane. These cells fail to regain normal shape even after oxygenation. As deformed cells cannot pass through small capillaries vaso-occlusion and ischemic necrosis of affected organ ensues. Environment of renal medulla is hypoxic and hypertonic and hence red cells are more prone to sickling here and cause renal damage progressively (Debaun, 2011). Apart from this hyper-filtration, hyper-perfusion injury also adds to progressive damage (Debaun, 2011 and Lanzkowsky, 2011). There is significant renal involvement in heterozygous statealso. State of art management of sickle cell anemia involves monitoring in specialty clinics, which aims at screening these children for different organ involvement and keeping the hemoglobin at an optimum level.

Corresponding author: **Bhushita Lakhkar**
Assistant Professor, India

Kidneys have been recognized to be an important organ which needs regular screening. Some authors observed that changes in renal doppler indices {resistive index (RI), Pulsatility index (PI)} occur earlier than rise in biochemical parameters like blood urea and serum creatinine (Taori, 2008 and Lakhkar, 2015) and hence this might be a better screening tool. It has been reported (Lakhkar, 2015 and Aloni, 2014), that in sickle cell anemia, initial renal damage is in the form of hyperfiltration injury, which causes increase in estimated glomerular filtration rate(GFR) and decrease in biochemical parameters like blood urea and serum creatinine.

This stage is followed by rise in these parameters above normal with advanced and irreversible renal damage .If renal involvement is detected early, precautions can be taken to avoid use of nephrotoxic drugs (like Non-steroidal anti-inflammatory drugs) which are very commonly used for painful crises. Present study is an effort to study the renal doppler indices (RI,PI) in sickle cell anemia patients with biochemically normal, lower than normal and above normal (high)renal function parameters. Detection of renal damage prior to irreversible changes (highbiochemical renal parameters) remained the main aim of study.

METHODS AND MATERIALS

Study settings: This prospective, cross sectional, observational study was conducted in the department of radio-diagnosis Acharya Vinoba Bhave rural hospital Wardha, Maharashtra.

Ethical clearance: was obtained from institutional ethical committee of a University in Sawangi (m) Wardha.

Study Period: Over 2 yrs, 108children with Sickle cell anemia were recruited.

METHODOLOGY

Selection criteria: Patients between 6 month to 50 yrs, diagnosed as sickle cell anemia (both homozygous and heterozygous) by Sickling test and hemoglobin electrophoresis were included. While recruiting homozygous patients it was made sure that patients were in steady state (asymptomatic for at least 2 weeks). These patients were registered cases in the sickle cell clinic run by the hospital. Patients having renal anomalies or without parental consent were excluded from the study. Demographic details of patients, presenting symptoms, signs, history of crises and blood transfusions were entered in a pretested, pre-validated proforma. Complete haemogram, renal function tests (Blood Urea and serum Creatinine), ultrasonography of kidneys were performed, which was followed by renal Doppler study. The results of investigations were compared with age specific norms (Debaun, 2011 and Lanzkowsky, 2011).

Ultrasound of kidney: All the patients were scanned by B mode Ultrasound with colour doppler ultrasound unit. A sector probe of frequency 3-5 MHz was used to evaluate abdominal organs and a linear probe of frequency 7-12 MHz was used to study the echo texture of various organs including kidneys in detail. Since the main pathophyiology in sickle cell disease occurs as a result of vascular obstruction by sickled red cells, the patency and resistance of renal vascular tree was evaluated with an ultrasound colourdoppler.

Renal doppler technique: Doppler sonography was performed on a colourdoppler ultrasound unit, Philips 11HdXE using a 3-5 MHz sector probe. The patients were examined in supine position, left lateral decubitus position for right kidney and right lateral decubitus position for left kidney. Doppler sonography was performed using non compression techniques and the waveforms were obtained from the main renal, segmental and inter-lobar arteries. Doppler parameters recorded were, resistive index (RI), pulsatility index (PI) and systolic/diastolic ratio(S/D).Three readings from each of the arteries in upper pole, mid pole and lower pole was taken and their average values were recorded. Renal dopplerresistive Index (RI) >0.7 and Pulsatility Index (PI)>1.14 was considered abnormal (Tublin, 2003 and Chavhan, 2008). Results were analyzed using SPSS software 23.Analysis using student t test was performed while comparing the means and proportions. P Value of <.05 was considered significant.

RESULTS

In the present study total of 108patients were recruited, out of which 73 patients (67.5%) were of sickle cellanemia (homozygous pattern) and 35 patients (32.4%) were of sickle cell trait(heterozygous pattern).Maximum patients belonged to the age groups of 10-19 yrs(39.8%) and 1-9yrs(37.9%) with the smallest number of patients in the age group of below 1yr and above 50yrs.Majority of patients were males (66.3%) and Male to Female ratio in our study was 2:1. Most patients presented with recurrent fever (63.8%), abdominal pain (47.2%) and recurrent joint pain (24%) during their previous visits. Symptoms were severe and common in homozygous patients, where as symptoms in heterozygous were nonspecific. During the recruitment patients were asymptomatic for at least two weeks. Most common crises were thrombotic crisis, mean rate of crises was 2/year, if age of patient was below 5 years and 5 /year between 5 to 15 years. After the age of 15 yrs crises became less common with crisis rate of around 1-2 /year. In the present study 38 patients (35.8%) had raised urea levels and 30 patients (28.3%) had raised creatinine level. Majority of patients (80%) having raised creatinine and urea values belonged to homozygous pattern. A group of homozygous patients(28 patients, 39%) and also heterozygous (4 patients,13%) had lower than normal serum creatinine. Few children in both groups(10%)also showed same trend with urea. These values mostly indicate hyper filtration. High Creatinine and urea levels were more common after 10 yrs, low values were common after 5yrs (Urea <5yrs 24+/- 4.32, 5 to 10 yrs 22 +/- 3.8 ,> 10 yrs 35+/- 9.49 mg/dl, creatinine < 5yrs (0.38+/-.08, 5 to 10yrs .22 +/- > 10 yrs 0.83+/- 0.27 mg/dl).This trend was seen in heterozygous patients also. Mean serum creatinine and urea level increased with age after 10 yrs. Renal ultra-sonography was found abnormal in 33(30%) patients in homozygous group and 4(5%) in hetero-zygous group. Most common findings were diffuse increase in echogenicity (58%) and small kidney (43%).Other findings included large kidney (20%), loss of cortico-medullary differentiation (17%), cortical scarring (12%) and thin parenchyma (5%). One patient had medullary nephrocalcinosis also. Most patients (85%) with ultrasound changes had high biochemical renal functions.

Renal Doppler: Renal indices were measured from main renal artery, segmental artery and interlobar artery. Earliest detection of abnormality and highest values were observed in interlobar arteries, which was the best vessel to study .If only main renal artery was studied 34% patients were missed .If only segmental artery was studied 23% patients were missed. In any age group mean renal indices were highest in interlobar arteries (p<.0.05). Overall renal doppler study was abnormal in 48 patients (43.6%) in SS type and in 15 patients (27.2%) in AS type (p=<.05) making total of 63patients (58%) with abnormal values. Most common age group with high RI and PIwas 5 to 14 yrs(66% showed increased RI, 56%showed increased PI) followed by 15 to 19 yrs(55%showed increased RI and 54%showed increased PI).In age group below 1 yr, RI and PI were high but it is considered normal for this age group hence was ignored[7].After the age of one year mean RI and PI values ,normally should come down to reach adult values, but in our patients it remained high. Mean RI value in the age group of 1 to 5 yrs was 0 .74,5 to 10yrs was 0.78 and above 10 yrs it was 0.82. Similar trend was seen with PI also(mean PI being 1.18 between 1 to 5 yrs,1.2 between 5-10 yrs and 1.21 above 10 yrs). Decrease inbiochemical parameters was described to be an early finding of renal damage in Sickle cell patients (Lakhkar, 2015 and Aloni, 2014). In the present study patients were divided into 3 groups based on high, low and normal biochemical parameters. PI and RI indices were compared in these groups. Mean PI and RI were higher in children with low biochemical parameters as compared to

children with normal biochemical parameters indicating more severe vascular changes. Both indices were highest in children with high biochemical parameters showing the correlation (Fig 1).

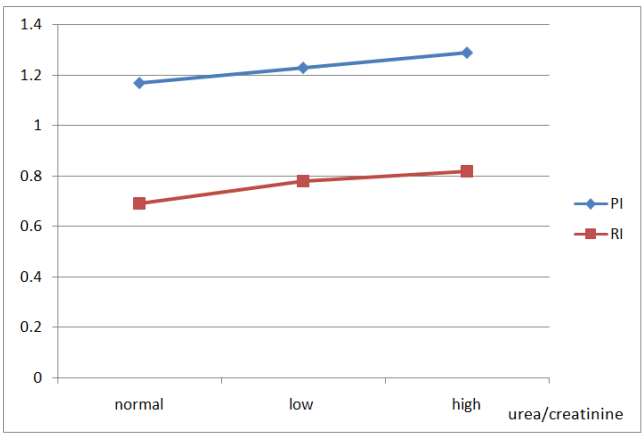

Figure 1. Correlation of mean PI and RI with Biochemical parameters

There were 38children with high biochemical parameters out of which 36 (95%)children had abnormal indices and 2(5%) had high normal indices,32 children had lower biochemical parameters of which20 (63%)had abnormal indices and 9 (28%) had high normal indices, among 38 children with normal parameters 7(18%) had abnormal indices 12 (32%) had high normal values (Fig. 2).

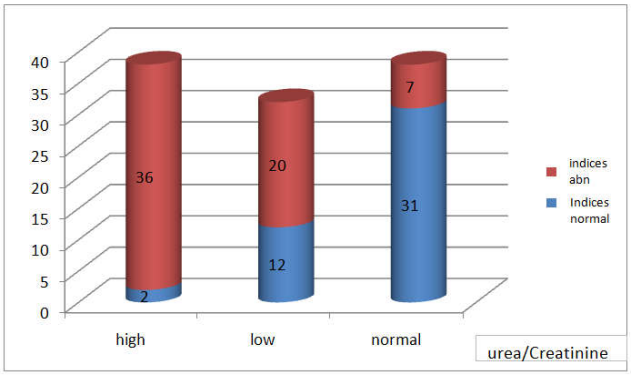

Figure 2. Correlation of No. of patients with abnormal doppler values with biochemical parameters

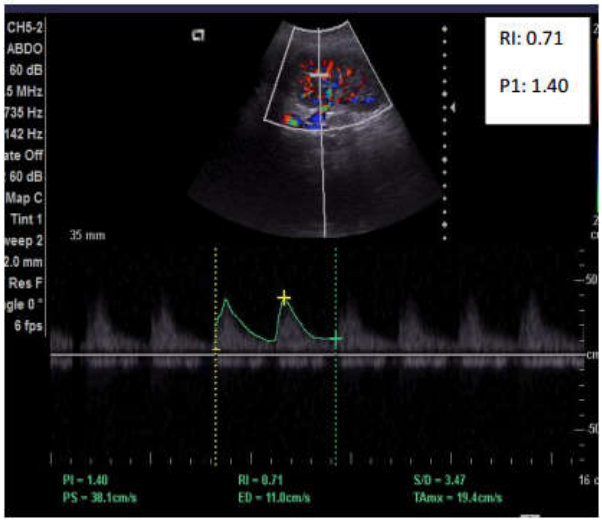

Image 1. Interlobar artery showing raise resistive and pulsatility index

These findings indicate that 27(25%) children could be diagnosed more when renal doppler indices are used to screen the children. Seven children (6%) with normal parameters and 20 (19%) children with lower than normal had abnormal indices and were detected before biochemical parameters became abnormally high.

DISCUSSION

Sickle cell anemia is very common in Vidarbhregion of Maharashtra and this area is popularly known as sickle belt. The tribal population in this area is highly affected (Colah, 2015). Wardha district occupies a part of this belt and Kamble etalobserved 5.7% (Kamble, 2000), of prevalence in hospitalized patients in this district. Similar situation exists in most hospitals in and around Wardha which includes our centre also. Frequently occurring crises leading to progressive organ involvement is common in sickle cell anemia. This clinical scenario necessitates regular monitoring for organ involvement to prolong the life and improve its quality in these children. Sickle cell specialty clinics are run by most government and other hospitals to take care of these children. Most of these clinics aim at optimising haemoglobin level by transfusions and protection from infections and crisis. Need for monitoring renal involvement has been recognized due to peculiar renal medullary environment making it prone for recurrent and progressive damage (Debaun, 2011). Monitoring using renal function test is invasive and it is late by the time these parameters are involved. As the damage in sickle cell anemia is due to vascular blockage and obstruction to the flow,use of renal doppler has been suggested (Taori, 2008; Chavhan, 2008 and Sarraf, 2009).

Renal damage in sickle cell anemia is progressive and increases with each renal crisis. The biochemical parametersofrenal function test has been compared during steady state and during crises (Lakhkar, 2015; Sarraf, 2009 and Guvenc, 2005). Significantly more children show abnormality during crisis than in steady state indicating some amount of recovery after crisis but the damage detected in steady state mostly persists (Lakhkar, 2015 and Sarraf, 2009). Hence in this study renal doppler study was carried out only in steady state. Study of estimated GFR and renal function tests in sickle cell anemia has been conducted by many authors (Lakhkar, 2015; Aloni, 2014).

It is reported that initially GFR increases and biochemical parameters like blood urea and serum creatinine decrease and subsequently with age GFR comes down and above parameters show significant rise. Most probable reason described is hyperfiltration and hyperperfusion of unaffected glomeruli which ultimately get damaged (Debaun, 2011; Lakhkar, 2015 and Aloni, 2014). This indicates lowering of Urea and creatinine may be the early stage of deterioration. This study correlates renal doppler indices with normal, low and high levels of biochemical parameters. It is observed that renal doppler indices becomes abnormal even when renal function parameters are normal (6% children) and more so when they are lower than normal (19% children) (Fig 1).This observation has not been reported earlier to the best of our search. Saraf et al described abnormal indices in children with high normal biochemical parameters (Sarraf, 2009). Another interesting phenomenon noticed in this study is, mean value of indices increased serially from normal biochemical paramaters to lower than normal parameters, reaching highest for patients

with high biochemical parameters. To the best of our knowledge this aspect also has not been studied (Fig 1,2). RI and PI indices in normal children is described to be specially high in the first year of life and then slowly comes down by the age of 6 yrs to reach adult values (Kuzmic, 2000 and Sıgırc, 2006). Murat etal. (Murat, 2005) found children above 3 yrs and adults had statistically insignificant difference in mean RI values. Kuzmic et al (Kuzmic, 2000), reported RI <0 .7 in all normal subjects above 6yrs. In our patients 58% patients (excluding children below one year) had values higher than adult normal cut off and in patients above 5 yrs 41% had abnormal RI values. Pulsatility index follows RI.

Conclusions

Study of renal indices in sickle cell patients is very useful in detecting early renal damage and interlobar artery is best to choose for it. In children between 5 and 10 yrs biochemical renal function parameters may be misleading as they may be below normal but renal indices become abnormal and help in early detection of damage. Serial Measurements of indices in patients attending sickle cell clinic can indicate early renal involvement if rising trend in values is seen.

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