ORIGINAL ARTICLE

Sonographic Screening for Abdominal Organ Involvement in Sickle Cell Anemia- A Step towards Better Patient Care

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Abstract:

Background: Sickle cell disease is characterized by repeated crisis and need for frequent transfusions. Abdominal crisis are common and potentially can damage any abdominal organ. Screening for organ involvement will lead to early detection and better patient care. *Aim and Objectives:* To see whether ultrasound can be a better noninvasive technique for early detection of organ involvement. *Material and Methods:* Prospective cross sectional observational study done on patients admitted in pediatric ward of a medical college. Total of 150 patients, already diagnosed to have sickle cell anemia (homozygous 110 and heterozygous 40) was included in the study. All the patients were in steady state. Demographic, clinical biochemical details were noted and were subjected to ultrasonography. Renal artery, Being end artery, Doppler study was also done. All the modalities were compared for early detection. *Results:* Majority of patients (77%) were between 1 to 30 years with male female ratio of 2:1. Recurrent fever (64%) and recurrent abdominal pain (47%) were most common symptoms and anemia (66%), hepatomegaly (62%), splenomegaly (21%) were most common signs. When clinical examination, biochemical tests and ultrasonography were compared for organ detection, ultrasound significantly detected more patients ($p=<0.05$). Ultrasonography of kidney included renal doppler also. Renal involvement by micro-albuminuria measurement was of same as ultrasonography. Organ involvement increased with age. *Conclusion:* Ultrasonography was good noninvasive technique for organ detection but kidneys yield was better with Doppler study. Most common organ found to be affected was liver. Involvement increased with age. Early detection helps clinicians to avoid drugs toxic to involved organs.

Keywords: Ultrasonography, Organopathy, Renal doppler

Introduction:

Sickle cell anemia is an inherited disease (autosomal recessive) due to abnormal hemoglobin chains within RBCs .This abnormality leads to rigid sickling of red blood cells as a result of repeated crisis which usually follow infections or hypoxia. These sickle shaped cells cause vascular occlusion and ischemia which leads to infarction in different organs of the body [1]. This phenomenon eventually results in to functional abnormality of the affected organs. The organs commonly involved are liver, spleen, kidneys, pancreas and gall bladder. The final word in sequence of organ involvement has not been found. Anemia in these patients results from hemolysis of abnormal cells and their removal from circulation by reticulo-endothelial system. Repeated transfusions may lead to iron overload which adds to derangement of organ functions [2]. Sickle cell anemia special clinics have been established in the hospitals situated in endemic areas. These clinics aim at prevention of infections (which lead to crisis) using penicillin prophylaxis, folic acid

supplementation for ongoing hematopoiesis, timely transfusion, monitoring for growth and iron overload. The life span of homozygous patients (SS type) is shorter than normal individuals due to major organ involvement and failure of their functions. Heterozygous patients (AS type) though often asymptomatic, are also known to have silent damage to different organs which remains undiagnosed till overt functional failure or complications ensue [1, 2]. The present study is an effort to find whether major organ involvement can be detected by a noninvasive technique (ultrasonography) prior to clinical and biochemical changes (functional involvement), to study correlation of functional organ involvement with age of patient and frequency of crisis. An early detection of organ involvement before functional derangement can guide the clinicians to adopt management techniques aiming at protection of involved organs thereby decreasing morbidity and mortality.

Material and Methods:

This is a prospective cross sectional observational study carried out over the span of 2 years (June 2012 - June 2015) in the department of Radio diagnosis, Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe) Wardha (Maharashtra, India). Ethical permission was obtained from Institutional Ethical Committee of Datta Meghe Institute of Medical Sciences (Deemed University). Total of 150 patients of sickle cell disease was enrolled in the study base on calculation of sample size using the formula Z^2pq/d^2 (Z= 1.96, p=prevalence, q=1-p; d=allowable error(5%)). As per selection criteria Patients diagnosed to have sickle cell anaemia (both Homozygous and heterozygous) by haemoglobin electrophoresis and attending sickle cell specialty clinic of the hospital were included in this study. Only steady state patients were included. Informed consent was obtained from all patients. Patients who not willing for consent or having systemic diseases affecting abdominal organs (like hypertension, diabetes) were excluded.

Demographic details of patients, presenting complaints, details about crisis/year, clinical examination findings were entered in a pre-validated proforma. All the recruited patients of sickle cell disease underwent ultrasound evaluation of upper abdomen. Ultrasound of pelvis was excluded.

Laboratory:

All the patients underwent complete haemogram (Total count, differential count, Platelet count) renal function test (Blood Urea, serum Creatinine), micro-albuminuria estimation and Liver function test (Alanine amino transferase {ALT}, Aspartate amino-transferase {AST}). Age specific normal values for different laboratory test were used for comparison [1, 2]. Urine for micro-albuminuria was analysed using PRIETEST eXP biochemistry analyzer and was considered positive when albumin in urine was between 30-300 mg/gm of creatinine [3].

Equipment:

Ultrasound

Patients were scanned by B mode Ultrasound using Phillips HD 11XE ultrasound and colour Doppler unit. A sector probe of frequency 3-5 MHz was used for abdominal organs and a linear probe of higher frequency 5-8 MHz was used to study the echo texture of various organs.

Patient Preparation

The patients were asked to fast for 3 hours whenever possible, to reduce bowel gas and prevent gall bladder contraction.

Patient Position

The examination was performed with patients in supine and lateral decubitus position to obtain an optimal view of the abdominal viscera.

Organ Ultrasound

Liver was scanned by a sub-costal approach and was measured in mid-axillary line. Liver echogenicity was judged by comparison with the cortex of the kidney. To measure spleen, patient was kept supine, the probe was angled between ribs inter-costally from postero-lateral approach and slowly the patient was rolled for better visualization. The echo-texture of spleen was compared to adjacent kidney. For the right kidney the patient was asked to lie supine and the probe was placed in the right lower intercostal space in the mid axillary line. For the left kidney right lateral decubitus position was used and probe was placed in lower intercostal space at posterior axillary line. If the renal cortex was brighter than liver / spleen it strongly suggested renal parenchyma disease.

Gall bladder was examined in a fasting state .The patient was scanned in at least two different positions sub-costally and or Inter-costally, which ever provided the best view. The pancreas was viewed with the patient in supine position. Erect views were used if colon gas obscured the view. Whenever the pancreas was obscured, patient was given a water load of 200-300ml. The pancreas usually is hyperechoic compared to the liver due to fat and was evaluated for any increase in size, altered echogenicity and calcifications within the parenchyma.

Renal Doppler:

In case of kidneys, Doppler study was also performed as vessels in kidneys are end arteries hence have role in preservation of function. The patients were examined in supine position, left lateral decubitus position for right kidney and right lateral decubitus position for left kidney. Non compression techniques were used and the waveforms were obtained from the main renal, segmental and inter lobar arteries. Parameters recorded were, Resistive Index (RI), Pulsatility Index (PI) and Systolic/Diastolic (S/D) ratio. Three readings from each of the arteries in upper pole, mid pole and lower pole were obtained and average values were recorded. Resistive index of 0.7 and pulsatility index of 1.14 was taken as cut off for abnormality [4].

Statistical Analysis:

Different methods of organ involvement were compared using Z score; P value below 0.05 was considered significant. Analysis was done using SPSS software of windows (17.0 SPSS, Chicago).

Results:

Total patients recruited were 150, out of which 110 patients were of homozygous pattern (SS type) and 40 patients were of heterozygous pattern (AS type). Patient characteristics are provided in Table 1. Symptoms were mainly present in SS type, AS type patients were either asymptomatic or had nonspecific symptoms (Table 1). Crisis was commonest between 5 to 20 years. Mean frequency of crisis was 4/year. Vaso-occlusive crisis was commonest (112 patients, 75%) and among vaso-occlusive crisis, abdominal crisis were commonest (60%).Homozygous patients received multiple transfusions and mean rate of transfusion was 3.4 per year. Liver function test were abnormal in 8 (5%) patients; two patients out of these were hepatitis B positive. In 34 (23%) patients AST and ALT were at a higher range. Mean ALT was 35.2 IU/L and Mean AST was 33.5IU/L. Twenty one patients (14%) had raised urea levels and 32 (21%) had raised creatinine level. The mean blood urea levels was 34 mg/dl and mean blood creatinine

levels was 0.9mg/dl. Majority of patients (80%) having raised Creatinine and urea values belonged to homozygous pattern. A group of patients 15 (10%) in SS type and 8 patients (5%) in AS type had lower than normal creatinine values. Few children showed same trend with urea also. These values mostly indicate hyper filtration injury. Abnormal serum creatinine and blood urea levels (high and low both) were common after 10 years of age. Mean serum creatinine and urea level increased with age (Urea < 5years 25+/- 4.32, > 10years 27+/-9.3 mg/dl, Creatinine < 5years 0.25+/-0 .08, > 10 years 0.63+/-0.27 mg/dl).This trend was seen in heterozygous patients also. Micro albuminuria was present in 10 patients (25%) of AS type and in 75% (82 patients) of SS type. It was also increased in frequency with age.

Organ Involvement

Clinical and Ultrasonography

Liver

Clinical hepatomegaly was found in 62 patients (41%), ultrasound detected 98 patients (65%) patients (Fig. 1). Five (3%) patients had firm hepatomegaly with Ultra-sonographic changes in echotexture and were diagnosed as cirrhosis, two among them were viral hepatitis and rest 3 had iron overload as these had high ferritin levels. Two patients had triangular hypo-echoic area with history of acute presentation and were diagnosed as hepatic infarction. All patients with liver involvement were above 11 years of age. Asymptomatic hepatomegaly with no echo-texture changes was seen in AS type patients.

Table 1: Showing Patient Characteristics (n=150)

Patient characteristics		**Number (Percentage)**
Age groups(yrs)	<1 1-9 10-19 20-29 30-49 50 and above	06(04) 41(27) 43(29) 32(21) 22(15) 06(04)
Sex*	Male Female	99(66) 51(34)
Historical data	Recurrent Fever Abdominal Pain (Recurrent) Joint Pain (Recurrent)	96(64) 71(47) 36(24)
Examination findings	Anemia Icterus Hypertension Hepatomegali Splenomegali	99(66) 04(2.6) 01(0.6) 62(41) 21(32)

**Male: Female Ratio – 1.94:1*

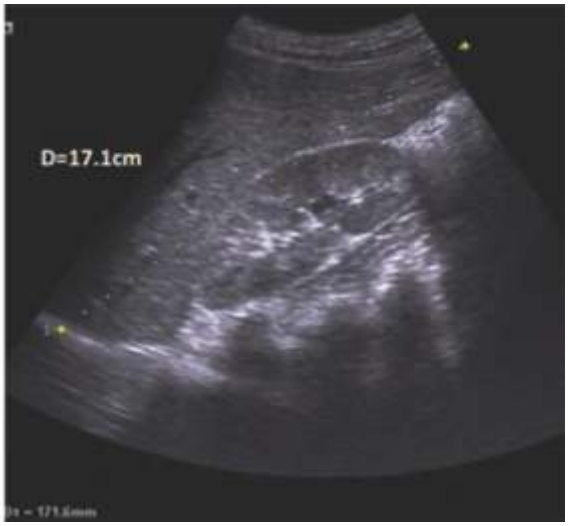

Fig. 1: Hepatomegaly

Kidney

It was next to liver as far as involvement is concerned (Fig. 1). Ultrasound findings in kidney are shown in table 2, Fig. 2a and Fig.2b. Ultrasonographic renal involvement was seen in 55 (36%) of patients. Renal doppler was abnormal in 90 patients (60%) out of which 15 (10%) were heterozygous and rest were homozygous. Patients who had high urea and creatinine (53 patients, 35%) or had sonographic changes all had abnormal doppler values. Twenty three patients who had lower than normal urea and creatinine also showed abnormal doppler values. Microalbuminuria estimation was abnormal in 95(63%) of patients. This was found to be equally (p= 0.90) sensitive test for renal involvement.

Table 2: Ultra Sonography of Kidneys in Sickle Cell Patients

Renal findings	SS type	AS type	Total (N=150)
Size enlarged	16	6	22(19)
Size reduced	52	3	55(37)
Decreased parenchymal thickness	08	0	08(5)
Diffusely increased echotexture	32	8	40 (27)
Medullary calcification	00	5	05(3)
Loss of cortico-medullary differentiation	25	0	25(17)
Cortical scarring	14	4	18(12)

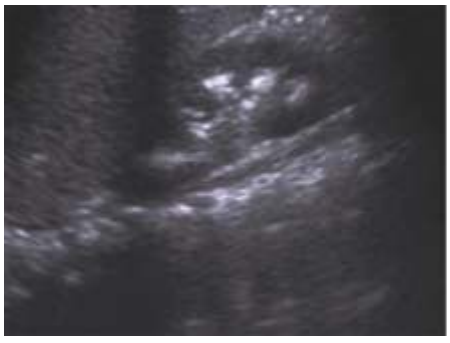

Fig. 2a: Medullary Nephrocalcinosis

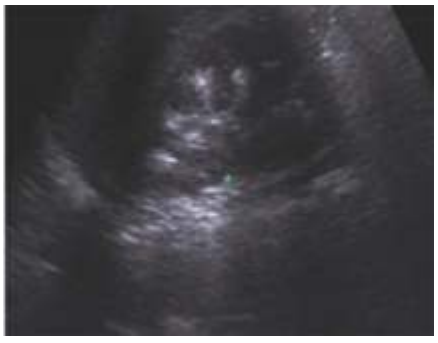

Fig. 2b: Medullary Nephrocalcinosis

Gall bladder

Around 11 % (16 patients) had cholelithiasis (Fig. 3 and Fig. 4) additional 6 % (9 patients) had biliary sludge. All except 2 patients with cholelithiasis and 5 patients with Sludge had increased gall bladder wall thickness (>3mm) indicating chronic cholecystitis. Only 2 patients had mucocoele and 2 had gall bladder Empyema (Fig. 5). One patient had acute Cholecystitis and needed surgery in emergency. Planned surgery was needed for mucocoele (2 patients), empyema (2 patients) and chronic cholelithiasis with recurrent colicky pain (7 patients). We did not find chole-docholithiasis or any other abnormality of common bile duct on ultrasound or even at surgery. Overall involvement of gallbladder was around 20%. Involvement of biliary systems increased with age. Youngest patient with liver involvement was 4 years old. Youngest patient with gall stones was 8 years old and 80% patients with stone were above 20 years.

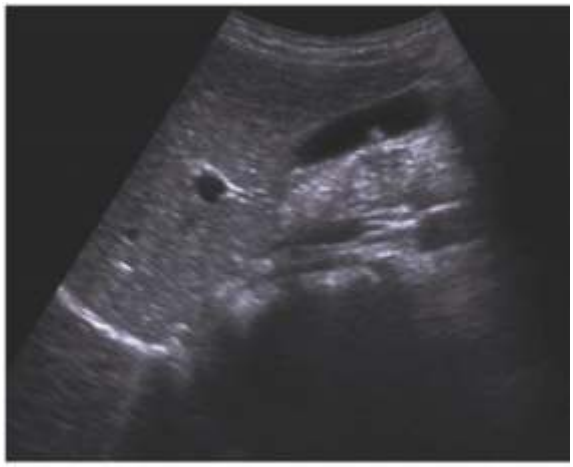

Fig. 3: Cholelithiasis

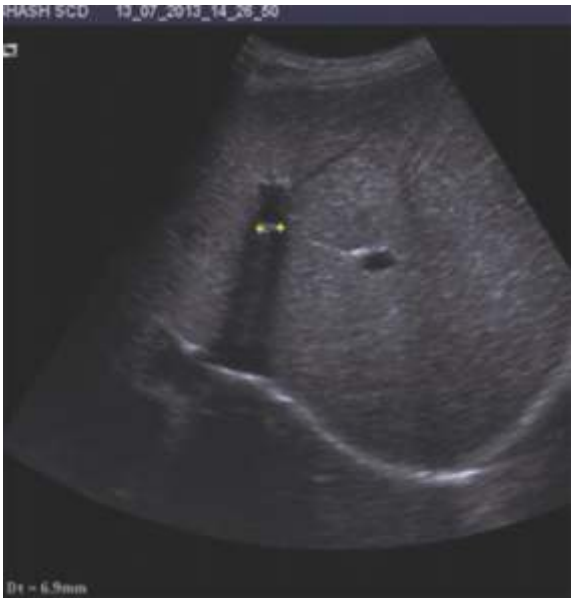

Fig. 4: Intrahepatic Biliary Radical Calculus

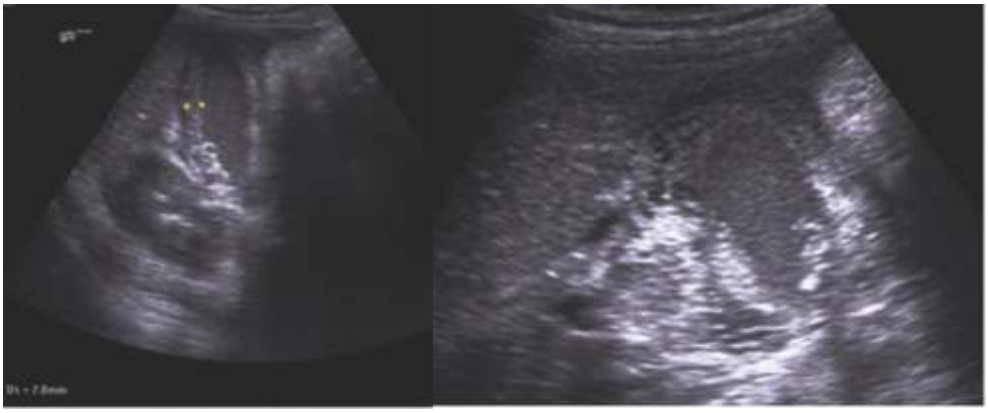

Fig.5: Empyema of Gall Bladder

Spleen

Clinically spleen was enlarged in 21(14%) patients and on ultrasound in 56 patients (37.3%). 34 (23%) patients had enlarged spleen and 10(7%) showed auto-splenectomy. Four patients (2.6%) had shrunken spleen, 6(4%) had infarction (Fig.6), 3 (2%) had splenic abscesses (Fig.7) and 9(6%) patients showed evidence of calcification. Among remaining patients with large spleen increased echogenicity was found. We could not do any splenic function test.

Pancreas

Changes in Pancreas were not noticed by us. When clinical laboratory and utrasonographic modalities for organ detection were compared, ultrasonography was most sensitive (p= <.05 for all organs except when compared to micro-albminuria) in Table 3.

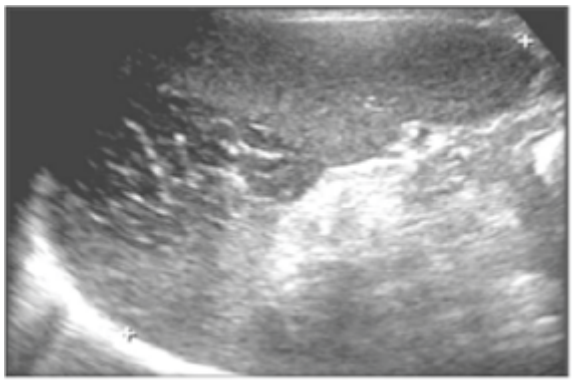

Fig. 6: Peripheral Wedge Shaped Hypo Density within Spleen – Infarct

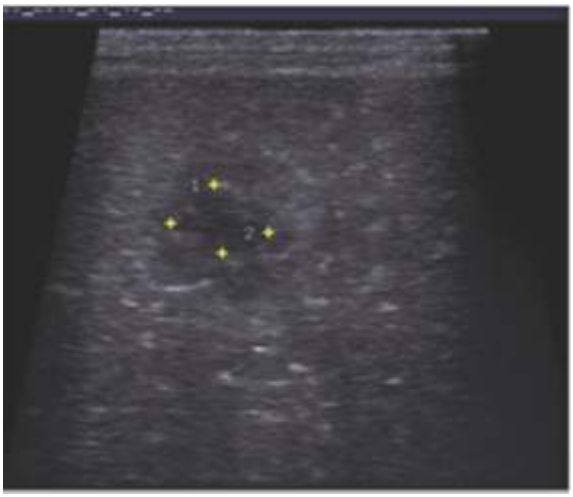

Fig. 7: Spleen Abscess - Ill Defined Hypoechoic Lesion in Spleen

Risk Factors for Organ Involvement

Homozygous /Heterozygous State

Homozygous state is the most important risk factor. Frequency and severity of organ involvement is more in SS type.

Correlation with Age

Organ involvement and its severity increased with age (Fig. 8). Organ involvement below 15 years and above 15years was compared using odds ratio at 95% confidence interval. Odds ratio for liver was 3.28 (p=0.01), for spleen 3.57 (p =0.006), for kidneys 4.2(p=0.01) and for gall bladder it was 6.16 (p =0.003).

Table 3: Organ Involvements in Sickle Cell Anemia by Different Methods

Organs	Clinical	Laboratory	Ultrasonography*	P value
Liver	62 (41)	08 (05)	98 (65)	0.0037^{S}
Spleen	21 (14)	-	56 (37)	0.0004^{S}
Kidney	01 (0.6)	53 (35), 92 (61) ı	90 (60)	0.0019^{S}, 0.9044^{NS}
Gall bladder	03 (02)	03 (02)	30 (20)	0.05S

**Renal evaluation by ultrasonography was inclusive of renal Doppler* ı *Micro-albuminuria*

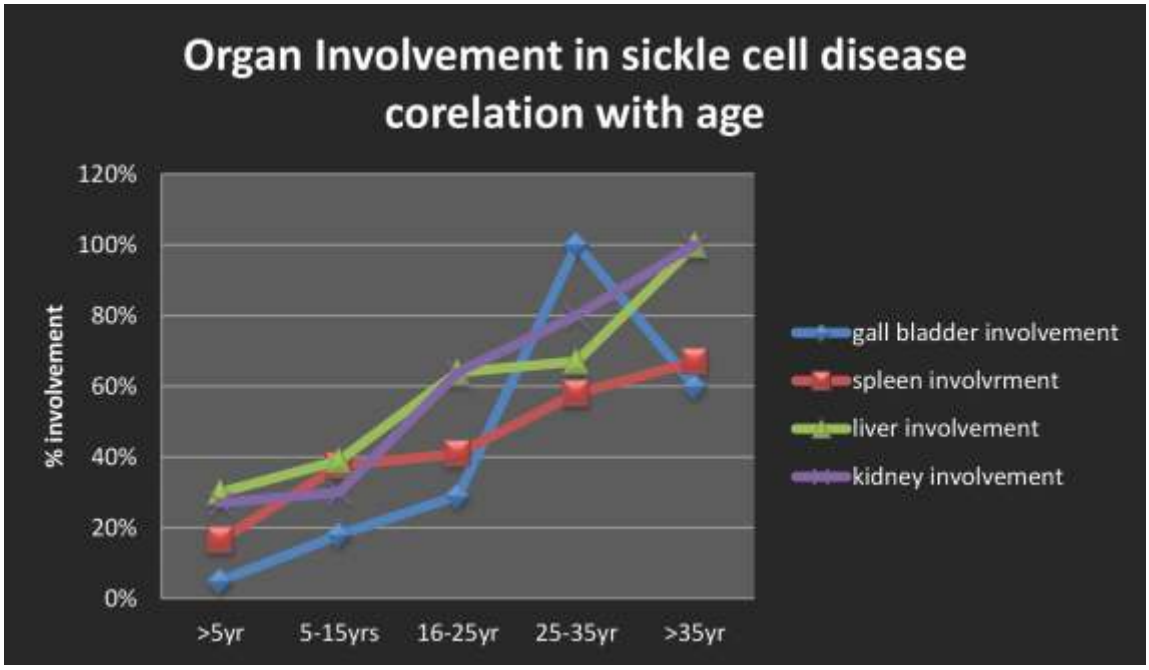

Fig. 8: Organ Involvement in Sickle Cell Disease Correlation with Age

Correlation with No of Crisis/Year

An attempt was made to correlate crisis with organ involvement. Patients especially after 20 years were not able to recall exact history of crisis. Only rough evidence could be collected by recall and available old papers. While crisis were more than 4/year, all 4 organ involvement and especially renal functional involvement was more (OR 1.8, p= <0.05). On the contrary in 10 patients where crisis were said to be less than 2/year quite severe organ involvement was found

Discussion:

Specialty clinics for sickle cell patients are a step towards reducing the morbidity and mortality. These clinics right now provide folic acid and Soda-bi-carb tablets, regularly evaluate hemoglobin status and also provide blood transfusion when indicated.

In order to further strengthen the clinics we should be able to predict and detect the problems early, thereby reducing the morbidity and death. Abdominal crisis is second most common crisis [1, 2]. Every crisis can potentially damage one or more abdominal organs. If major abdominal organs can be screened by a non-invasive, it will go long way in helping these patients and clinicians. Many institutes use blood investigations to detect organic problems hence this study also correlates ultrasound and organ function tests where ever possible.

Liver

Liver was most commonly involved organ like other studies [6-10]. Authors have quoted involvement ranging from 59 % to 100%. In most studies the criteria to say liver involvement was hepatomegaly on ultrasound, one study used clinical and biochemical modalities like present study [8]. We found 65% involvement mostly in homozygous children .Involvement was more if age group was higher (more than 10 years).

Detection rate by liver function test was lowest in our study and in other studies also [8]. Echotexture changes were seen in few patients in our study and same was true in others also [11-13]. Bright liver and abscesses described by other studies [13-14] were not found by us. Early detection of liver involvement may guide the clinician to avoid hepato-toxic drugs like acetaminophen so often needed during crisis.

Kidneys

Ultrasonographically shrunken kidney was most common (37%) and only 19% had large kidneys in our series. Ali Balci [10] studied 102 patients and 30% had large kidneys, Ibinaiye [13] studied 74 patients and 27% had small kidneys. In sickle cell anemia, increased Glomerular Filtration Rate (GFR) and large kidneys has been described in early age due to hyperfiltration, later in life the GFR comes down and renal size becomes small [14]. Difference in our findings and other authors [10-13] was mostly due to age group studied.Diffusely increased echogenicity was next common finding (27%) in our patients and 30% of these patients had abnormal renal functions. Ibinaiye *et al*. [13] and Balci [10] found increased (medullary or diffuse) echogenicity in 18.9% and 15.7% patients respectively. Focal hyper-echoic areas (3.3%) found by Bakhita *et al*. [15] and Medullary calcinosis found by us was not found by others. Overall ultrasonographic findings in kidney are not very common (36% in our series) and its correlation with functions also is not very good. It is difficult to say which change is a predictor for chronic renal failure.

As the main mechanism for organ damage in sickle cell anemia is vaso-occlusion, renal doppler was tried by many authors [16-18].We also used renal doppler in our patients. Renal doppler was more useful than ultrasound (36% Vs 62%, p = 0.001) as it was positive in 62% patients. Similar results were obtained by Taori et al [15] and others also [17-18]. Micro-albuminuria as a test for early detection of renal involvement is equally sensitive when compared to doppler (61.3%, 60%, p= 0.09)) but this test may not be available everywhere.

Spleen

Spleen has tortuous micro-circulation which causes stasis and has hypoxic, hyperosmolar media for process of sickling, as a result repeated infarctions are common leading to fibrosis, shrunken spleen and auto-splenectomy [19]. In early age increased spleen volume has been described by McCarville *et al* [19] and others also [13].We also observed this phenomenon. Auto-splenectomy in other studies ranged from 4% to 47% (10, 12-14). Mostly the age of patient recruitment makes this difference. We had more patients in younger age group hence shrunken spleen was found in only 2.7% and auto-splenectomy in only 7% cases. Echo-textural changes of infarction, abscesses indicate various stages towards auto-splenectomy. Autosplenectomy reduces the need of transfusion with increasing age [1-2] but increases the chances of massive infections. Early detection of this phenomenon will help clinician to start penicillin prophylaxis in selected patients before infection occurs.

We could not correlate functional and ultrasonographic spleen involvement; McCarville *et al* [14] did not find correlation with splenic sonographic changes and radionuclear (99c) liver - spleen scan.

Gall bladder

It was the least affected organ (20%). In our series 12 patients (40%) were symptomatic and needed surgery. Similar findings are reported by Curro *et al* [20]. We found cholilithiasis in 11 % of patients,

others [13-14] have reported higher prevalence of 25 -30%. We noticed sludge in 6% of patients where as above authors reported in fewer patients (4.1, 2.8%). Sludge is a known precursor of gall stones. Age of patients may be responsible for this difference in prevalence, which is mentioned by Walker TM also [21]. Avoiding drugs like Ceftriaxone can reduce the chances of sludge formation. It is one of the common drugs used in sickle cell anemia patients.

Thickness of gall bladder wall which is usually associated with gall stone is thought to be due cholecystitis or may be due to vaso-occlusion leading to oedema. Chronic hemolysis leads to pigment stones [21] and stasis of content due to stone might contribute to Cholecystitis.

Pancreas

Changes in pancreas have been reported due to iron deposition following transfusion. We did not find any pancreatic findings but others [10, 13] have reported increased echogenicity and punctate echogenic foci in pancreas.

Risk factors

Homozygous state and age as risk factor has been found by other authors also [21]. Heterozygous patients though asymptomatic may have silent organ involvement as shown in present study and other studies [10]. Most special clinics run by different hospitals only involve homozygous patients. Ultrasound abdomen and renal Doppler both can help in follow up of AS type patients also.

In the present study some correlation of organ involvement has been found with number of crisis per year, but was difficult to correlate severity of involvement. Some patients with less number of crisis showed more severe involvement. Possibility of silent infarctions can explain this phenomenon. If this is true then it further emphasizes importance of follow up specially using ultrasound.

Conclusion:

Ultrasound is a sensitive and early method to detect organ involvement. Liver is the most common organ involved. Detection of renal involvement can be improved if renal doppler is used. Early detection of organ involvement can help clinician to avoid using toxic drugs like Ibuprofen, other hepato-toxic drugs and decide about penicillin prophylaxis. Follow up of AS type sickle cell patients also are essential to avoid late problems.

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