Document heading doi: 10.21276/apjhs.2018.5.4.9 Original Article

A study on C-reactive protein as an early marker of vasococclusive crisis in sickle disorders

Kausik Goswami[1], Anindya Sasmal[2*], Sheela Kandulna (Goswami)[3], Prakash Chandra Panda[4], I R Agrawalla[5], Sukanta Sen[6]

[1]Assistant Professor, Department of Pediatrics, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal 721645, India
[2]Assistant Professor, Department of Radiodiagnosis, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal 721645, India*
[3]Assistant Professor, Department of Pediatrics, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal 721645, India
[4]Associate Professor, Department of Paediatrics, Veer Surendra Sai Institute of Medical Sciences and Research, PO-Burla, Dist. Sambalpur, Odisha 768017, India
[5]Professor, Department of Paediatrics, Veer Surendra Sai Institute of Medical Sciences and Research, PO- Burla, Dist. Sambalpur, Odisha 768017, India
[6]Professor, Department of Pharmacology, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal 721645, India

Received: 15-09-2018 / Revised: 25-10-2018 / Accepted: 10-11-2018

Abstract

Background: Sickle cell disease (SCD) patients often seek care in the Emergency Department (ED) due to vaso-occlusive crisis (VOC), the most common complication of SCD. Currently, no diagnostic test can determine if a SCD patient is having an acute VOC. **Methodology:** Irrespective of the clinical diagnosis and type of sickle cell crises the confirmation of haemoglobin pattern in sickle cell disease patients and healthy subjects were done by sickling test, hemoglobin electrophoresis or high performance liquid chromatography. **Results:** Irrespective of age and sex, most common variety of vaso-occlusive crisis was bony crisis including hand foot syndrome. About 91.2% patients demonstrated CRP positivity during the early phase of vaso-occlusive crisis. Subsequently the CRP positivity rate declined in the mid phase (28%) and late phase (2.4%) of vaso-occlusive crisis reflecting response to therapy. There is a significant difference of CRP status between non vasoocclusive and vaso–occlusive crisis of sickle cell disease patients. About 96.3% patients of non vaso-occlusive crisis became CRP negative during their whole course of their crisis**. Conclusion**: Analysis of large number of cases with sickle cell vaso-occlusive crisis with quantitative serial measurement of CRP level is needed for better evaluation of patients during prodromal phase for effective and better management of these patients.

Keywords: Sickle cell disease, vaso-occlusive crisis, C-reactive protein, marker, sickling test, hemoglobin electrophoresis, high performance liquid chromatography.

Introduction

Sickle cell disease (SCD) is one of the most common monogenic disorders globally with an autosomal recessive inheritance. This disorder is haemolytic in nature; it is a genetic disorder in which two abnormal genes are inherited from both parents.

**Correspondence*
Dr Anindya Sasmal
Assistant Professor, Department of Radiodiagnosis, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal 721645, India
E-Mail: dr.asasmal2009@gmail.com

It was first reported by J. B. Herrick (1910) among the African Negroes. Sickle cell disease is one of the grand disease in terminology of Victorian pathology because of its wide spread and molecular defect in sickle cell hemoglobin as described by Ingram (1956) is substitution of valine for glutamic acid at 6^{th} position of β chain of haemoglobin. Sickle haemoglobin is abnormal due to point mutation in gene coding for it. The normal codon GAG at position β^6 of globin mRNA is replaced by GUG (Marrotta et al 1977)[1-3].

Several studies have reported regarding increased prevalence of this disease among the people of Orissa, especially in western part. In

Orissa high prevalence is seen among people of Agharia (30.6%), Kulta (9.4%), Tanti (18.4%) and among many other tribal casts as per previous studies (Kar BC et al 1986; Kar BC 1991). Crisis is different types like vaso-occlusive crisis or painful crisis, hyper-haemolytic crisis, aplastic crisis and sequestration crisis. The most important predisposing factors for various crises are infection, dehydration, acidosis, exhaustion, atmospheric temperature variability, emotional and psychological disturbance etc.[4-6]

Patients with sickle cell disease have intermittent painful crisis caused by occlusion of microcirculation with sickled cells. Crisis varies considerably in severity ranging from mild episodes that respond at home to simple analgesics and oral rehydration to extensive tissue infarction requiring parental opiates and intravenous fluid in hospital.

V.S.S. Medical College is situated in Western Orissa and cater to a population of 6 – 8 millions of adjoining districts and also part of Chhatisgarh. Large number of patients of sickle cell haemoglobinopathy attends paediatric Outdoor and Indoor. Considering the magnitude of this disease in this area this study was undertaken with following aim and objectives to find out the value of measurement of acute phase reactants like C-reactive protein as an objective marker of tissue ischemia during steady state, as an early marker in the diagnosis of vaso-occlusive crisis in sickle cell disorder and on response to treatment.

Materials & Methods

This study was conducted in the Outdoor and Indoor patients of paediatric department and sickle cell clinic of V.S.S. Medical College, Burla. Study subjects in the age group of 6 month to 14 yrs were enrolled in the study. The study subjects were divided into 5 separate group as per case definition specified.

Inclusion Criteria

- **Group I:** It includes patients of electrophorectically or high performance liquid chromatographically proved cases of homozygous sickle cell disease (HbSS) and sickle β thal disease (Hb S- β thal) who were in the steady state. Steady state means – Crisis free period extending for at least 3 weeks since last clinical event and 3 months or more since last blood transfusion before the start of new clinical events.
- **Group II:** It includes patients of electrophorectically or high performance liquid chromatographically proved cases of homozygous sickle cell disease (HbSS) and sickle β thal disease (Hb S- β thal) presenting with vaso-occlusive crisis of any variety.
- **Group III:** It includes patients of electrophorectically or high performance liquid chromatographically proved cases of homozygous sickle cell disease (HbSS) and sickle β thal disease (Hb S- β thal) presenting with any crisis other than vaso-occlusive crisis.

Exclusion Criteria

Patients of acute rheumatic fever, collagen vascular disease, infective hepatitis, infective endocarditis, portal hypertension, recent typhoid vaccination and meningitis were excluded from the study group.

Methodology

Irrespective of the clinical diagnosis and type of sickle cell crises the confirmation of haemoglobin pattern in sickle cell disease patients and healthy subjects were done by sickling test, hemoglobin electrophoresis or high performance liquid chromatography. After careful selection of cases a detailed history and thorough clinical examination was done. In each case the following investigations were done as required for the study.

Hematological Investigations

A. Routine Hematological Investigations

a. Sickling Test: The sickling phenomenon was demonstrated by following methods. A drop of capillary blood was obtained by finger prick and. taken over a clean glass slide. A cover slip was put over it and carefully sealed with Vaseline. This preparation was kept at room temperature for 24 hrs and then examined under microscope to detect presence of sickled erythrocyte.[7]

b. Haemoglobin Estimation (Hb%), differential count and comment on peripheral smear, total leucocyte count (TLC), total rbc count (TRBC), packed cell volume (PCV), erythrocyte sedimentation rate (ESR), total platelet count (TPC) and reticulocyte count was estimated in all the cases.[7]

B. Special hematological investigations: Were done as and when necessary

a. Haemoglobin Electrophoresis

The principle of Hb-electrophoresis at alkaline pH is based on the alteration of haemoglobin molecule which follows certain amino acid substitution. In practice the method requires a source current, a buffer system and a supporting medium. Haemoglobin electrophoresis on acid agar gel provides valuable confirmatory and additional evidence. It is done in a citrate buffer at pH 6.0 to 6.2. HbF migrates slightly towards cathode and HbS and HbC towards anode, whereas most other variants remain in position of HbA close to the origin. The use of both alkaline and acid agar gel electrophoresis serves to identity HbS and HbC separately and indicates presence of less common variants[7-8].

b. Estimation of foetal haemoglobin (Batke method)

0.6 ml of prepared hemolysate was taken with 10 ml of Drabkins solution and was allowed to stand for 10 minutes. This mixture is called Cyanmeth haemoglobin (HICN). 5.6 ml of HICN was taken and 0.4 ml of 1.2 N sodium hydroxide was added to it. It was allowed to mix well for 2 minutes. Then 4 ml of saturated ammonium sulphate solution was added to it and mixed well. The mixture was filtered. The filtrate was compared with standard using green filter calorimeter with light of wave length 540 µ. **Standard:** 1.4 ml of HICN was taken in a test tube and 1.6 ml of distilled water was added to it. Then 2ml of saturated ammonium sulphate solution was added and mixed well. 0.5ml of the mixture was taken in to 4.5 ml of Drabkins solution and was compared in the calorimeter in green filter with the test. **Calculation:** (Reading of test x 5)/Reading of standard = % of HbF

c. Semiquantitative Estimation of C-reactive protein

Semiquantitative estimation of C-reactive protein estimation was done by diagnostic kit manufactured by Span Diagnostic Ltd. (Surat, India) by rapid latex slide technique.

Principle: This test based on the immunologic reaction between CRP as an antigen and latex particles have been coated with monospecific anti-human CRP and sensitized to detect levels greater than 6 µg/ml CRP. The latex slide test has the advantage of rapid performance in comparison to other tests for detection of CRP.

Sample: 5-10 ml venous blood was collected into sterile tube/vial without anticoagulant. Sample was allowed to clot at room temperature for several hours. After complete formation of clot serum was separated and was stored at 2-4°C.

Reagents / Accessories (Supplied in the Kit)

Reagent 1: CRP Latex Reagent

Reagent 2: Positive Control Serum

Reagent 3: Negative Control Serum

Use of Controls: Positive and Negative Controls are not always required when the reagents are in continuous use as the variety of specimens being tested will ensure both agglutinated and nonagglutinated patterns frequently. However, such controls are provided in the kit for performing an occasional check. It is, therefore, not necessary to run Positive and Negative Controls with every test[9-10].

Procedure

Qualitative Slide Test

All reagents as well as the sample were allowed to reach room temperature:

Using the disposable plastic dropper, one drop of undiluted test serum was placed within the circled area on the special slide provided in the kit. One drop of Latex CRP Reagent (the vial was shaken gently immediately before use) was added to the one drop of undiluted test serum and was mixed well with a disposable applicator stick and was spread out to the edge of the test area. The slide was rocked gently to and fro for 2 minutes and was examined for macroscopic agglutination under direct light source. **Note:** For positive and negative controls, the same procedure was followed as mentioned above by taking pre-diluted control serum from respective vials. **Note:** Controls were not diluted.

Interpretation: Qualitative Slide Test:

Observation

Conclusion

i) Coarse agglutination: Strongly positive

ii) Finer agglutination: Weakly positive

iii) Smooth suspension without : Negativeany noticeable change

d. Other tests done: Blood pH Estimation by using pH Meter, serum bilirubin, arterial blood gas analysis, blood culture and sensitivity, slide for malaria parasite, quantitative buffy coat (QBC) test for malaria parasite, immuno chromatographic test (ICT) for malaria parasite and routine urine & stool examination, X-ray chest, ultrasound of abdomen and Mantoux Test.

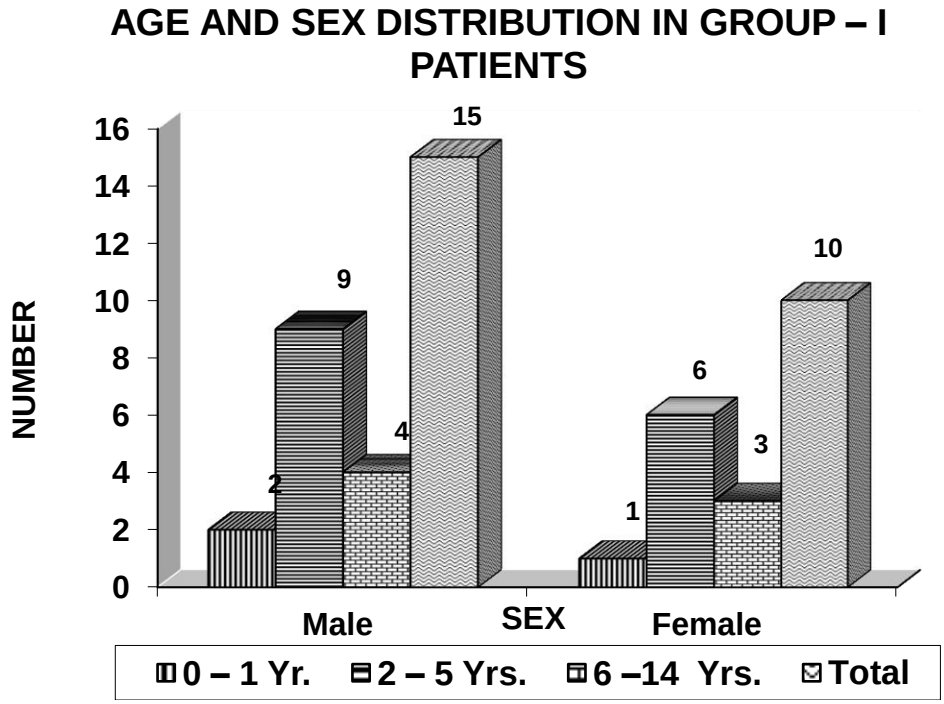
In **Group I** total 25 patients were followed up by regular check up and by doing semi quantitative estimation of C-reactive protein every four monthly in their steady state. Initially 37 patients were enrolled but due to appearance of crisis or irregular follow up only 25 could satisfy the inclusion criteria of minimum of 3 steady state CRP reports out of a maximum 6.

In **Group II** total 50 patients were taken as study subjects and semi quantitative estimation of C-reactive protein were done on early (day 1–3), middle (day 4–7) and late (day 7 onwards) phase of vaso-occlusive crisis. Initially 56 cases were enrolled in this group but we have to drop out 6 cases due to appearance of both vaso-occlusive and non vaso-occlusive crisis.

In **Group III** total 20 patients were selected and their C-reactive protein status were studied on early (day 1 - 3), middle (day 4 – 7) and late (day 7 onwards) phase of crisis. Initially 28 patients were enrolled in this group but 8 cases were excluded due to presence of vaso-occlusive and non-vaso-occlusive crisis.

Results

Figure 1: Age and sex distribution among Group I study participants



There were 15 (60%) male and 10 (40%) female patients enrolled in Group – 1. Largest number of cases 15(60%) were between 2 – 5 yrs of age. The male patients outnumbered the female patients with a ratio of 1.5: 1 [Fig. 1].

Table 1: Steady state CRP positivity in Group – I patients (n=25)

Age (yrs)	Sex	No of patients	CRP status	
			Positive (>6mg/l)	Negative (<6mg/l)
0 – 1	Male	02	0	02
	Female	01	0	01
2 – 5	Male	09	0	09
	Female	06	0	06
6 -14	Male	04	0	04
	Female	03	0	03
Total		25	0	25

Table 1 shows that number of patients were being CRP positive or negative during their steady state throughout the study period. It shows that regardless of age and sex patients were in 100% CRP negative status during their steady state.

Table 2: Type of vaso-occlusive crisis in Group – II patients [n=50]

Type of presentations	No of patients			% of Prevalence
	Male	Female	Total	
Hand foot syndrome	04	02	06	12
Other bony crisis	12	08	20	40
Abdominal crisis	05	04	09	18
Hepatic crisis	03	03	06	12
CNS crisis	01	01	02	04
Splenic crisis	01	01	02	04
Acute chest syndrome	02	03	05	10
Total	28	22	50	100

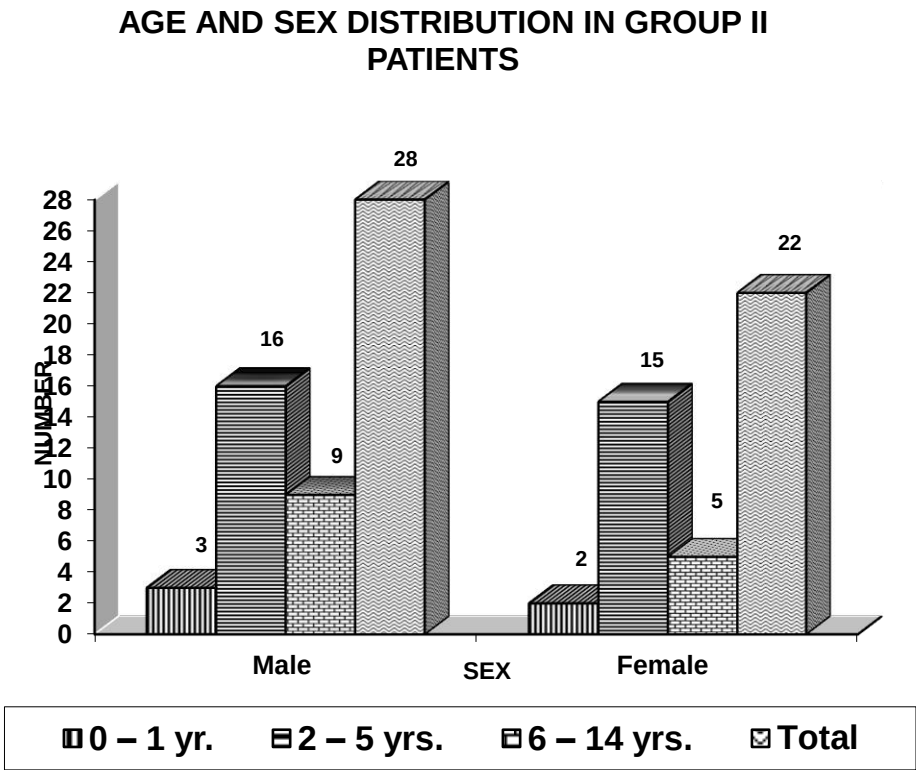


Figure 2: Age and sex distribution among Group 2 study participants

There were 28 (56%) male and 22 (44%) Female patients enrolled in Group II. Largest number of patients 31 (62%) were between 2–5 year of age. The male patients outnumbered the female patients with a ratio of 1.27:1 [Table 2/ Fig. 2]. Bony crisis including hand foot syndrome was the commonest mode of presentation of vaso-occlusive crisis encountered in 26 (52%) of cases. Next common modes of presentation were abdominal crisis (18%) and hepatic crisis (12%). Acute chest syndrome was not very uncommon (10%). CNS crisis and splenic crisis were rare. There were no case of ocular crisis, renal crisis and priapism reported during study period [Table 2].

Table 3: CRP status in early phase of different types of vaso-occlusive crisis in Group – II patients [n=34]

Type of crisis	No. of patients	CRP status							
		Positive (> 6 mg/l)				Negative (< 6 mg/l)			
		M	F	T	%	M	F	T	%
Hand foot syndrome	04	03	01	04	100	00	00	00	00
Other bony crisis	15	07	07	14	93.3	01	00	01	6.7
Abdominal crisis	06	01	03	04	66.7	01	01	02	33.3
Hepatic crisis	04	03	01	04	100	00	00	00	00
CNS crisis	01	01	00	01	100	00	00	00	00
Splenic crisis	01	00	01	01	100	00	00	00	00
Acute chest syndrome	03	01	02	03	100	00	00	00	00
Total	34	16	15	31	91.2	02	01	03	8.8

Though we enrolled total 50 patients in this group but in early phase only 34 cases were reported at the hospital. Irrespective of age and sex distribution maximum number of patients who presented in the early phase of vaso-occlusive crisis was CRP positive. Total no. of CRP positive cases in this phase was 31 (91.2%) and CRP negative cases were 3 (8.8%) [Table 3].

Table 4: CRP status in middle phase of different type of vaso-occlusive crisis in Group – II patients

Type of crisis	No. of pt.	CRP Status							
		Positive (> 6 mg/l)				Negative (> 6 mg/l)			
		M	F	T	%	M	F	T	%
Hand foot syndrome	06	01	00	01	16.7	03	02	05	83.3
Other bony crisis	20	02	01	03	15	10	07	17	85
Abdominal crisis	09	01	01	02	22.2	04	03	07	77.8
Hepatic crisis	06	01	01	02	33.5	03	01	04	66.5
CNS crisis	02	01	01	02	100	00	00	00	00
Splenic crisis	02	00	00	00	00	01	01	02	100
Acute chest syndrome	05	01	03	04	80	01	00	01	20
Total	50	07	07	14	28	22	14	36	72

Irrespective of age and sex distribution CRP positivity rate was low in the middle phase. Total no of CRP positive cases in this phase were 14 (28%) and CRP negative cases were 36 (72%) [Table 4].

Table 5: CRP status in late phase of different type of vaso-occlusive crisis in Group – II patients [n=41]

Type of crisis	No. of pt.	CRP Status							
		Positive (> 6mg/l)				Negative (< 6mg/l)			
		M	F	T	%	M	F	T	%
Hand foot syndrome	02	00	00	00	00	02	00	02	100
Other bony crisis	16	00	00	00	00	10	06	16	100
Abdominal crisis	09	00	00	00	00	05	04	09	100
Hepatic crisis	06	00	01	01	16.7	03	02	05	83.3
CNS crisis	02	00	00	00	00	01	01	02	100
Splenic crisis	02	00	00	00	00	01	01	02	100
Acute chest syndrome	04	00	00	00	00	01	03	04	100
Total	41	00	01	01	2.4	23	17	40	97.6%

CRP status among the total 41 patients during late phase (day 7 onwards) of vaso-occlusive crisis was estimated. Though we enrolled total 50 patients, in this group only 41 cases were available during late phase of crisis because of nine drop outs which includes 2 deaths, 4 lost to follow up and 3 patients left the hospital without any information.

Maximum number of patients irrespective of their age and sex became CRP negative during late phase of crisis or remission phase of crisis. In this phase total no of CRP positive case was only 1 (2.4%) and total no of CRP negative cases were 40 (97.6%) [Table 5]. There were 9 (45%) male and 11 (55%) female patients enrolled in Group III. Largest number of patients 10 (50%) were between 6-14 yrs of age followed by 8 (40%) were between 2-5 yrs of age. The female patients outnumbered the male patients with a ratio of 1.2: 1. This showed that non vaso-occlusive crisis was equally prevalent in either sex between 2–5 yrs and 6–14 yrs of age group [Fig. 3].

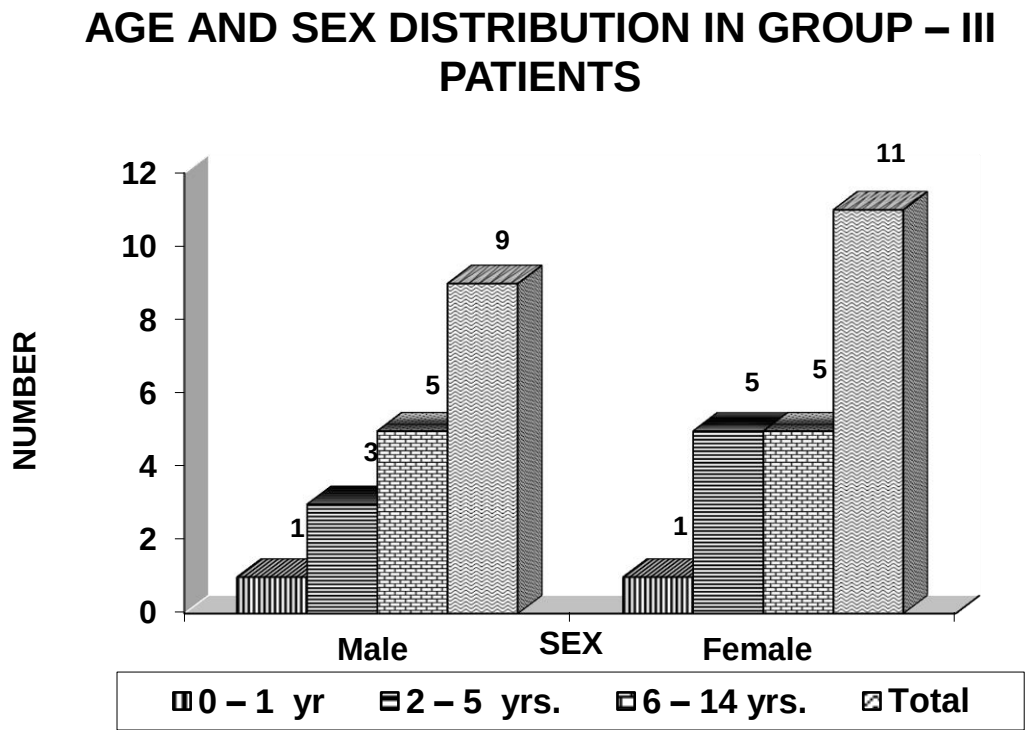


Figure 3: Age and sex distribution among Group III study participants

Table 6: Type of non vaso-occlusive crisis in Group III patients [n=20]

Type of crisis	No of patients		Total	Percentage
	Male	Female		
Aplastic crisis	02	01	03	15
Hyper haemolytic crisis	05	10	15	75
Sequestration crisis	02	00	02	10
Total	09	11	20	100

Regardless of age and sex hyper haemolytic crisis (75%) was being most common type of non – vaso-occlusive crisis followed by aplastic (15%) and sequestration (10%) crisis [Table 6].

Table 7: CRP status in early phase of non vaso-occlusive crisis in group III patients (n=13)

Type of crisis	No. of pt.	CRP Status							
		Positive (> 6mg/l)				Negative (< 6mg/l)			
		M	F	T	%	M	F	T	%
Aplastic crisis	02	00	00	00	00	02	00	02	100
Hyper haemolytic crisis	09	00	00	00	00	04	05	09	100
Sequestration crisis	02	00	00	00	00	02	00	02	100
Total	13	00	00	00	00	08	05	13	100

CRP status in the early phase of non vaso–occlusive crisis among 13 Group III cases was analyzed. Though total 20 cases were enrolled in group III, only 13 cases were reported during early phase of non vaso-occlusive crisis. It showed that 100% patients were CRP negative during early phase of non vaso-occlusive crisis irrespective of their age & sex [Table 7].

Table 8: CRP status in middle phase of non vaso-occlusive crisis in Group III patients [n=18]

Type of crisis	No. of pt.	CRP Status							
		Positive (> 6mg/l)				Negative (< 6mg/l)			
		M	F	T	%	M	F	T	%
Aplastic crisis	03	00	00	00	00	01	02	03	100
Hyper haemolytic crisis	15	01	01	02	13.3	04	09	13	86.7
Sequestration crisis	00	00	00	00	00	00	00	00	00
Total	18	01	01	02	11.1	05	11	16	88.9

CRP status in middle phase of non vaso – occlusive crisis among 18 Group III patients was analyzed. Though total 20 cases were enrolled in this group, 2 cases of sequestration crisis who presented during early phase, died after 2 days of hospital admission. It showed that only 2 (11.1%) cases became CRP positive during middle phase of crisis but 16 (88.9%) cases still remained CRP negative [Table 8].

Table 9: CRP status in late phase of non vaso-occlusive crisis in Group III patients [n=16]

Type of crisis	No. of pt.	CRP Status							
		Positive (> 6mg/l)				Negative (< 6mg/l)			
		M	F	T	%	M	F	T	%
Aplastic crisis	01	00	00	00	00	01	00	01	100
Hyper haemolytic crisis	15	00	00	00	00	05	10	15	100
Sequestration crisis	00	00	00	00	00	00	00	00	100
Total	16	00	00	00	00	06	10	16	100

Among the 20 patients enrolled, 2 cases of sequestration crisis and 2 cases of aplastic crisis died during the hospitalization. It appeared that 100% patients became CRP negative in the late phase of crisis [Table 9]. Another comparison is done between the two groups of patients i.e. Group II (During vaso-occlusive crisis of sickle cell SS and Sβ thal disease patients) and Group III (During non vaso-occlusive crisis of sickle cell SS and Sβ thal disease patients). CRP status in both these groups were studied in three phases early (day 1 –3), middle (day 4 – 7) and late (day 7 onwards). It was found that in group II 91.2% patients in early phase, 28% patients in middle phase and 2.4% patients in late phase became CRP positive. So in the case of vaso-occlusive crisis it was noted that maximum percentage of patients become CRP positive at the onset of crisis. Gradually they had became CRP negative in middle and late i.e. remission phase of crisis.

It was found that in Group III 100% patients in early phase, 88.9% patients in middle phase and 100% patients in the late phase became CRP negative. So in the case of non vaso-occlusive crisis maximum percentage of patients became CRP negative throughout the course of their non vaso-occlusive crisis.

So by comparing these two groups and by doing statistical analysis it was observed that CRP status is a good marker to know the onset of vaso-occlusive crisis and subsequently CRP status (negativity) is a good marker to know the resolution of vaso-occlusive crisis and the response to treatment but CRP negativity cannot exclude the occurrence of other crises. So by applying following method, we found out the utility of CRP level estimation during the prodromal phase of vaso-occlusive crisis.

Table 10: Screening test

Screening test (CRP status)		Vaso-occlusive crisis		Total
		Yes	No	
+ve	21	17	04	21
-ve	29	04	25	29

$$\text{Sensitivity} = \frac{17}{17+4} = \frac{17}{21} x100 = 85.7\%$$

$$\text{Specificity} = \frac{25}{25+4} = \frac{25}{29} x100 = 86.2\%$$

$$\text{Positive predictive value} = \frac{17}{21} x100 = 85.7\%$$

$$\text{Negative predictive value} = \frac{25}{29} x100 = 86.2\%$$

$$\text{\% of false negative} = \frac{4}{21} x100 = 19.05\%$$

$$\text{\% of false positive} = \frac{4}{29} x100 = 13.7\%$$

Discussion

Present study showed that number of patients was being CRP positive or negative during their steady state throughout the study period. It shows that regardless of age and sex patients were in 100% CRP negative status during their steady state. A. Singhal and GR Serjeant (1993) by their study reported that percentage of CRP positivity among sickle cell patient is 18% during their steady state who were symptomless for preceding 2 weeks. The present study enrolled sickle cell patients who were symptomless for preceding three weeks and did not receive blood transfusion for preceding 3 months. This probably accounts for very high level of steady state CRP negativity here[11].

In the present study bony crisis including hand foot syndrome was the commonest mode of presentation of vaso-occlusive crisis encountered in 26 (52%) of cases. Next common modes of presentation were abdominal crisis (18%) and hepatic crisis (12%). Acute chest syndrome was not very uncommon (10%). CNS crisis and splenic crisis were rare. There were no case of ocular crisis, renal crisis and priapism reported during study period.

Konetey–Ahulu (1974), Serjeant (1970) observed polyarthralgia as a presenting feature of bony crisis in sickle cell vaso-occlusive crisis[12-13]. Incidence of bony crisis as reported by Konoteny - Ahulu (1974) is 89.4%[12]. Serjeant (1985) also reported that prevalence of bony crisis is very high among Indian sickle cell patients during his study with incidence of

hand foot syndrome being 20%. The present study demonstrated prevalence of bony crisis as 40% and hand foot syndrome as 12%[14].

Abdominal crisis and splenic crisis presenting as acute abdominal pain had been observed by Handerson (1950) and Diggs (1965) during the vaso-occlusive crisis in sickle cell patient. Similarly Praharaj (1969) have reported 25% of abdominal crisis in his study series. Nanda BK et al (1967) reported, 20% of splenic crisis presenting as abdominal pain during his study. Prevalence of abdominal and splenic crisis was 18% and 12% respectively in the present study[15-18].

Eva Svarch et al (2001)[19] studied the incidence of acute chest syndrome in sickle cell patients of Cuba and reported a prevalence of 22%. In current study prevalence was 10%. Though ocular crisis, renal crisis and priapism is not very rare in African sickle cell children as told by Talbot JF (1988)[20] these three varieties of crises are rare in Indian sickle cell children (Kar BC et al 1986)[4]. Not a single case of ocular crisis, renal crisis or priapism was detected during the ongoing study.

Maximum number of patients irrespective of their age and sex became CRP negative during late phase of crisis or remission phase of crisis. In this phase total no of CRP positive case was only 1 (2.4%) and total no of CRP negative cases were 40 (97.6%). Akinola (1992) studied CRP level among 20 patients of sickle cell anaemia with vaso – occlusive crisis. He found that out of 20 patients, 15 patients were CRP positive (75%) on day 1 of crisis and became CRP negative after 7 day of onset of crisis[21].

J. Stuart, P.C.W Stone (1994) studied measurement of CRP level among 14 established cases of vaso–occlusive crisis. They reported in their study that C-reactive protein increases early in the crisis in near about 98% of cases. But in majority (78%) cases whose crises subsided within 3 days showed a fall of C-reactive protein after 2–3 days of onset of crisis. They found in 2 (14%) cases whose crisis persisting for more than 7 days became CRP positive till day 8 of crisis[22].

Eva Svarch et al (2001) after their study regarding the elevation of CRP during vaso – occlusive crisis of sickle cell disease children in Cuba reported that among 83 patients, they found increased C – reactive protein in 100% of them during early phase of crisis but CRP positivity in 15% of them during late phase of crisis. Among the 20 patients enrolled, 2 cases of sequestration crisis and 2 cases of aplastic crisis died during the hospitalization. It appeared that 100% patients became CRP negative in the late phase of crisis[19].

Akinola NO, Stevens SM (1992) also described similar type of prodormal phase in vaso-occlusive crisis. They reported in their study that in 60% of sickle cell patients' CRP level was increased during prodormal phase as compared to their CRP level in Steady state and these percentage of patients ultimately developed vaso-occlusive crisis 6-7 days after the rise of CRP level and subsequently as crisis evolved, these patients' CRP level became decreased to normal steady state CRP level[21].

JF Dohery, A Singhal and GR Serjeant (1993)[11] also by their studies reported that during monitoring of steady state C-Reactive patients in sickle cell patients 54% developed increased levels of CRP. They followed up these patients and saw that ultimately these patients developed vaso-occlusive crisis during follow up. They also described this phase of steady state as prodromal phase of vaso–occlusive crisis.

P Hernandez, Eva Svarch (2001)[19] studied 83 patients with sickle cell anaemia and they found increased C-reactive protein in 55% of them during the steady state and they found during the follow up of these patients that these 55% patients developed vaso-occlusive crisis within 4-5 days of CRP positivity.

Conclusion

The most common crisis in sickle cell disease is vaso-occlusive crisis which may have various modes of presentation starting from hand foot syndrome to ocular crisis. If early intervention is not done during tissue ischemia or infraction due to vaso-occlusive crisis, it will increase the morbidity in sickle cell disease patients by persisting sequelae of different organ damage. If vaso-occlusive crisis can be diagnosed as early as in prodromal phase, extent of tissue ischemia can be minimized by early institution of therapy. There is no significant difference between steady state CRP status in sickle cell disease patients and healthy AA patients. CRP status as an early marker during prodromal phase of vaso-occlusive crisis was found out to be having 85.7% sensitivity, 86.2% specificity, 85.7% positive predictive value, 86.2% negative predictive value with percentage of false negativity 19.05% and percentage of false positivity 13.7%. Analysis of large number of cases with sickle cell vaso-occlusive crisis with quantitative serial measurement of CRP level is needed for better evaluation of patients during prodromal phase for effective and better management of these patients.

References

1. Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. 1910. Yale J Biol Med. 2001 May-Jun;74(3):179-84.
2. Ingram V.M. A specific chemical difference between globins of normal and sickle-cell anemia hemoglobins. Nature 1956; 178: 792-794.
3. Marrotta CA, Wilson JT, Forget BG. Human β Globin messenger RNA nucleotide sequences derived from complementary DNA. J Biochem 1977; 252: 5040-5051.
4. Kar BC, Satapathy RK, Kulozik AE, Kulozik M, Sirr S, Serjeant BE, et al. Sickle cell disease in Orissa State, India. Lancet. 1986; ii: 1198–201.
5. Kar BC. Sickle cell disease India. J Assoc Physicians India. 1991 Dec; 39(12):954-60.
6. Serjeant GR, Ghosh K, Patel J. Sickle cell disease in India: A perspective. The Indian Journal of Medical Research. 2016; 143(1):21-24.
7. Schimidt RM, Brosius EM. Center for disease control bureau of laboratories haematology division. 7th edition. 1975. Basic laboratory methods of hemoglobinopathy detection.
8. Junius GA, Martin H. Laboratory detection of hemoglobinopathies and thalassemias, in Hematology Basic Principles and Practice, H. Ronald, B. J. Edward, J. S. Sanford, F. Bruce, and J. C. Harvey, eds., Churchill Livingstone, London, 1991, 1815–1827.
9. Richards NP, Elliott TS, Powell RJ, O'Callaghan C, Franklin P. Can the rapid semiquantitative estimation of serum C reactive protein be adapted for the management of bacterial infection? Journal of Clinical Pathology. 1985; 38(4):464-467.
10. Vallance H1, Lockitch G. Rapid, semi-quantitative assay of C-reactive protein evaluated. Clin Chem. 1991 Nov; 37(11):1981-2.
11. Singhal A, Doherty JF, Raynes JG, McAdam KP, Thomas PW, Serjeant BE, et al. Is there an acute-phase response in steady-state sickle cell disease? Lancet. 1993 Mar 13; 341(8846):651-3.
12. Konty-Ahulu F. The sickle cell disease clinical manifestation including sickle cell crisis. Arch Int. Med 1974; 133:611.
13. Serjeant GR. The clinical features in adults with sickle cell anaemia in Jamaica. West Indian Med J. 1970 Mar; 19(1):1-8.
14. Serjeant GR. The clinical features of sickle cell disease. Oxford Med. Publications; 1985.
15. Handerson AB. Sickle cell anemia; clinical study of fifty-four cases. Am J Med. 1950 Dec; 9(6):757-65.
16. Diggs LW. Sickle cell crisis. Am. J. Clin Pathol 1965; 44:119.
17. Praharaj KC, Mohanta KD, Kar RS, Swain U, Nanda BK. Haemoglobinopathy in Orissa. Indian Pediatr. 1969 Aug;6(8):533-7.
18. Nanda BK, Panda GK, Naik UP, Nankda CN, Prharaj KC. Haemoglobin-S in Agharia community of Orissa. J Indian Med Assoc. 1967 Feb 16;48(4):150-2.
19. Svarch E, Hernández P, Ballester JM. Sickle Cell Disease in Cuba. Available at http://bioinformatica.uab.es/biocomputacio/treballs00-01/cuaresma/a%20Cuba.htm [Accessed on 12 Sept, 2018]
20. Talbot JF, Bird AC, Maude GH, Acheson RW, Moriarty BJ, Serjeant GR. Sickle cell retinopathy in Jamaican children: further observations from a cohort study. Br J Ophthalmol. 1988 Oct; 72(10):727-32.
21. Akinola NO, Stevens SM, Franklin IM, Nash GB, Stuart J. Rheological changes in the prodromal and established phases of sickle cell vaso-occlusive crisis. Br J Haematol. 1992 Aug; 81(4):598-602.
22. Stuart J, Stone PC, Akinola NO, Gallimore JR, Pepys MB. Monitoring the acute phase response to vaso-occlusive crisis in sickle cell disease. J Clin Pathol. 1994 Feb; 47(2):166-9.

Conflict of Interest: None
Source of Support: Nil