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Study of Pulmonary Complication due to Embolism in Sickle Cell Disease

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Abstract: ***Background**: Children particularly affected by sickle cell disease (SCD), there is dearth of research on this topic in India, specifically targeting the magnitude of SCD-related complications. We therefore conducted this study to determine the burden of acute chest syndrome (ACS) and describe its clinical and therapeutic aspects among SCD children. **Methods**: This study was carried-out from January 2015 to May2016.Weenrolled all SCD children with confirmed diagnosis of ACS, and recorded their clinical presentation at admissionalong with their evolution during hospitalization. **Results**: 28 cases of ACS were identified during the study period, from 258 hospitalizations of childrenwith SCD. Ages ranged from 11 months to 18 years. We noticed relatively low levels of HbF, from 5.5 to 13.5 % with a mean of 13.5 % (5.9%).The three main symptoms at admission were fever (53.5 %), cough (46.5%) and chest pains (28.5 %). Two patients (7.1%) developed ACS 2 days after admission. The main localizations of radiological alveolar consolidations were the lower lobes. The duration of hospitalization, the mean of which was 6.8 (3.1) days, was influenced by none ofthe tested variables (p values > 0.05). **Conclusion**: ACS is frequent among SCD children's. Its etiologies seem to be multifactorial. Patients'parents should be educated to recognize early signs and symptoms of the disease, and consult rapidly.Additionally, clinicians must be trained to diagnose ACS, and manage it promptly and efficiently to avoid its relatedcatastrophic consequences.*

Keywords: Sickle cell disease (SCD); acute chest syndrome (ACS); Children; HbF

1. Introduction

One of the devastating autosomal recessive disease that results in the substitution of valine for glutamic acid at position six of the beta – globulin gene results in a condition which makes the red blood corpuscles sickle shaped. If the condition is homozygous for the HbS gene then the condition is known as sickle cell diseaseand if the condition is heterozygous then it is called as sickle cell trait. In India the condition is commonly seen in Orissa, Maharashtra, Jharkhand ,Chhattisgarh and other parts central India .The hydrophobic interactions between the adjacent molecules in oxygen deficient state is the result of such abnormal HbS gene.

When deoxygenated condition persists sickle haemoglobin which is the result of abnormal genes leads to polymerisationwhich makes the red blood corpuscle change its shape to sickle shaped or elongated rod shaped corpuscle which makes the red blood corpuscle almost impossible to pass through the minute arterioles resulting in vascular accidents [1]. The vascular accidents and the destruction of the corpuscles are the clinical features of SCD.The other symptoms are painful episodes due to ischaemia. The other features of the disease depend on the organ systems involved. The changes in red cell membrane results in the altered function, The red blood corpuscle becomes more affinated to vascular endothelium and this forms the basis of plaque formation restricting the blood flow to the different tissues of the body[2-3].

Acute chest syndromes, Abnormal renal functioning, painful muscular dystrophies, neurovascular complications are some of the conditions which are the result of sickling.[4, 5].ACS is an acute lung injury syndrome that occurs frequently in patients with SCD. Indeed, it is the second mostcommon cause of hospitalization, and the leading cause ofdeath, contributing to almost 25 % of SCD-related mortality[6, 7]. Moreover, nearly half of deaths due to ACS occur inSCD patients less than 20 years of age [8]. Repeatedepisodes of ACS negatively impact long-term lung function,resulting thereby in chronic lung diseases [9].

Pulmonary findings on chest X-ray consistent with alveolar consolidation with any of the clinical symptoms may be useful in diagnosing the ACS.Charache et al. [10] first suggested using the term "acute chest syndrome" for this complication. ACS may be more severe in individuals with HbSS as compared with HbSC disease [6, 7, 11–14].

One major cause of the ACS is from HbS-containing erythrocytes [6, 11, 15]. Currently there are no conclusive randomized controlled clinical trials to guide therapy [16]. The most common practise is vastly symptomatic treatment. Treatment largely includes analgesics, broad-spectrum antibiotics, bronchodilators, oxygen to maintain saturation, and blood transfusions [6, 11, 17, 18].

The study puts in a sincere effort to learn the different diagnosing and therapeutic methods which can be useful for the practising doctors and paediatricians.

2. Subjects and methods

This was a retrospective study conducted from January 2015 to May2016 .We participants aged below 18 years were included in the study. These were known SCD children and adolescents with a confirmed diagnosis of ACS.The diagnosis was based on X – Ray in which the consolidation was prominent. The demographic patterns like socio – economic status and past history was taken into account. The patients in whom the X Ray finding was negative was not included in the study.

3. Statistical Analysis

Statistical analyses used SPSS, version 20.0. Results are expressed as mean (Standard Deviation). p value < 0.05 was used to characterize statistically significant results.

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4. Results

We recorded on the whole 28 cases of ACS during the study period, on 258 hospitalizations of children with SCD, hence an in-patient prevalence of 10.8 %. Table 1 displays the study population's general profile. Ages ranged from 11 months to 16 years, with a mean of 5.5 (3.4) years, and males were more represented than females.

Table 1: General profile population

Characters		*Numbers (n=28)*	*Percentage (%)*
Age	0-5 years	16	57.1%
	>5 years	12	42.8%
Sex	Male	21	75%
	Female	7	25%

Only seven patientshad a hemoglobin electrophoresis dating back to less thanone year, HbS ranging from 51 % to 56 % with a mean of 76.2 (11.8) %, and HbF, from 5.5 % to 19.5 % with a mean of 13.5 (5.9) % (Table 2). Only 38.1 % of children wereregularly followed-up, i.e. were used to visiting the unit fora check-up at least every 3 months. Besides, not morethan 33.3 % of our patients had been adequately vaccinated in accordance with their ages.

Results of biological tests showed very high levels of leukocytes, neutrophils, serum CRP and serum LDH. Indeed, their mean values were 31543.9 (17562.8)/mm3, 25613 (12354.2)/mm3, 223.8(123.2) mg/l, and 5231.7(2715.3) IU/l respectively. Contrariwise, we observed relatively low levels of hemoglobin, with a mean of 3.54(6.25) g/dl (Table 2).

Table 2: Summary of quantitative variable

Variable	Min	Max	Mean	SD	Median	IQR
Age (years) n=28	0.82	18	4.5	3.2	6.2	3.2-5
Hbs (%) 9	51	56	76.2	11.8	44.2	62-65
HbF (%) 9	5.5	19.5	13.5	5.9	13.2	9.7-19.3
Leucocytes (/mm^3) n=17	9456	72655	31543.9	17562.8	30526	19532-32564
Neutrophils (/mm^3) n=16	4300	52611	25613	12354.2	21500	11233-28355
Haemoglobinemia (g/dl) n=18	3.8	8.2	3.54	1.057	6.25	5.3-7.5
Serum LDL (UI/l) n=16	1352	9652	5231.7	2715.3	2035	1563-5693
Serum CRP (mg/l) n=15	3.9	412	223.8	123.2	223.5	86-402

Table 3: Clinical features of ACE

	Number (n=28)	Percentage (%)
Duration of evaluation of symptoms before consultation		
≤ 48 hours	9	31.1 %
> 48 hours	19	67.8 %
Symptoms motivating consultation		
Fever	15	53.5
Cough	13	46.4
Thoracic pain	10	28.0
Generalized pain	5	17.8
Abdominal Pain	2	7.1
Dyspnea	8	28.5
Clinical Sign		
Altered general appearance	12	42.8
Pulmonary Consolidation	12	42.8
Clinical anaemia	8	28.8
Respiratory distress	6	21.4
Jaundice	2	7.1
Hemoglobinuria	1	3.5
Result of the chest X ray		
Right upper lobe consolidation	3	10.7
Right middle and lower lobes	2	3.5
Consolidation		
Right lower lobe consolidation	15	53.5
Left lower lobe consolidation	5	17.8
Right and left lower lobes	6	21.4

According to our patients' parents, duration of evolution of symptoms before consultation ranged from less than 24 h to almost 14 days, with a mean of 4.8 (4.2) days. The presenting complaints are reported in Table 3. The three main symptoms were fever (67.8 %), cough (53.5 %), and chest pains (17.8 %). The main clinical signs we observed were pulmonary consolidation (42.8 %), an altered general appearance (42.8 %), clinical signs of anemia (28.8 %), and signs of respiratory distress (21.4 %). Two patients (9.5 %) who were initially admitted for vaso-occlusive crises (VOC) developed ACS after 2 days of hospitalization.

The main localizations of radiological alveolar consolidations were the lower lobes (10.7 %).Right middle and lower lobes (3.5 %), Right lower lobe consolidation (53.5 %), Left lower lobe consolidation (17.8 %) and Right and left lower lobes (21.4 5 ; Table 3).

5. Discussion

This study showed that ACS accounted for 10.8 % of SCD children hospital admissions with almost 4.1 SCD patients presenting ACS per month. This proportion is comparable to the 1.9 ACS episodes/month among hospitalized SCD children in Bruxelles [15]. However, our prevalence of ACS is lower than the 10–20 % rate of hospital admissions reported by Miller and Gladwin in their review [6]. Our prevalence may be an underestimate of the real burden of ACS among children suffering from SCD for some reasons. As we considered only known SCD patients, some unknown SCD patients may have presented this condition and escaped from enrolment, due to parents' financial constraints, we are used to performing just one chest x-ray during hospitalization. As a result, we could have missed all those whose first chest x-ray was normal but who developed ACS later on, given that radiographic findings in case of ACS may progress over time [9, 11, 19]. If it is true that a positive chest x-ray is the key element to define the disease [12], there have been some claims that a single negative chest x-ray cannot exclude the disease, taking into account that clinical assessment may appear inadequate to identify ACS [11]. It has been also suggested that every SCD patient presenting with fever must undergo a chest x-ray [11, 20].

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Consequently, close clinical monitoring alongside serial radiographic evaluation is necessary. In fact, it has been shown that ACS may develop 1 to 3 days after admission for VOC as there may exist a close relationship between ACS and VOC [6, 11, 15]. This is truer for adults than children, as the latter usually present with ACS at admission. In our study for instance, only 2 children (7.1 %) developed ACS 2 days after admission, and pains were concomitantly associated in 52.4 % of cases. Some risk factors involved in the development of ACS during hospital stay have been identified such as the male sex, past medical history of ACS, thoracic pains at entry and use of morphine during hospitalization [15].

Although we did not assess risk factors of developing ACS, we observed a male predominance and relatively low levels of HbF, in line with the literature [6, 16, 17]. We also found that fever (67.8%), cough (53.4 %) and thoracic pains (17.8 %) were the main symptoms in keeping with previous reports [9,], these symptoms being mainly in favour of pulmonary infections. Despite the fact that we did not have our patients' baseline leukocyte counts, we noticed very high leukocyte counts [31543.9 (17562.8)/mm3], especially neutrophils [25613 (12354.2)/mm3], associated with elevated serum CRP levels [223.8 (123.2) mg/l]. These elements are also strongly suggestive that infection may initiate or precipitate the development of ACS among our patients, corroborating previous reports elsewhere [15, 16]. However, though blood culture was not performed in all patients, no germ was identified. This result was also reported by Neocleous et al. [20] who incriminated rib infarction as the main etiology of ACS. But without invasive procedures, it is very difficult to rule out conclusively a bacterial infection as a cause of ACS. Microorganisms that have been identified associated with ACS include Streptococcus pneumonia, Chlamydiae pneumonia, Mycoplasma pneumonia, influenza virus A H1N1, parainfluenza virus, respiratory syncytial virus and coronavirus among others [15].

6. Conclusion

ACS is frequent among SCD childrens. Its etiologies seem to be multifactorial including infection, pulmonary thrombosis and fat embolism. After an initial normal chest x-ray, especially in a patient presenting with VOC, repeated clinical evaluation must be conducted and possible changes in the clinical status should indicate the necessity of a new radiographic examination. Patients' parents should be educated to recognize early signs and symptoms of the disease. Additionally, clinicians must be trained to correctly diagnose ACS, and manage it promptly and efficiently to avoid its related catastrophic consequences.

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