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Evaluation of pulmonary function in Egyptian children with sickle cell disease: a single center study

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Abstract

Background Among inherited blood diseases, sickle cell disease (SCD) is the most common, and its prevalence is rising worldwide. People with SCD often have abnormal lung function, which can lead to other health problems and a lower quality of life. This study investigated the lung function problems in Egyptian children with SCD.

Methods Our study is cross-sectional analytic, held in the pediatric pulmonology and hematology specialized clinics of Abulrish Children's Hospital, Faculty of Medicine, Cairo University. A detailed history was taken; then, patients underwent spirometry.

Results A total of 60 children in the steady state were recruited, 58% males and 42% females; 73% of the study population was homozygous SS, 22% was SB^{+}thalassemia, and 5% was SB^{0} with a mean age of 11.4 years. Spirometry done to the patients showed that 17 of the studied 60 sickle cell patients (28%) exhibited impaired pulmonary functions primarily with a restrictive pattern (16.7%).

Conclusion This study has shown that lung function problems are common in Egyptian children with sickle cell disease (SCD). Restrictive lung disease was predominant in our cohort. Therefore, regular yearly screenings using spirometry might be beneficial for early detection. Additionally, close monitoring by a pediatric lung specialist is recommended.

Keywords Sickle cell anemia, Spirometry, Pulmonary functions, Restrictive lung disease

Background

Respiratory diseases are widely responsible for morbidity along the course of sickle cell disease (SCD) [1]. Airway involvement is seen in SCD with repeated attacks of acute chest syndrome (ACS), airway obstruction without the presence of allergy-related bronchial asthma, or hyper-responsive airways [2].

The underlying cause of pulmonary involvement in SCD may differ from allergy-related bronchial asthma, indicating airway inflammation caused by vaso-occlusive events or hemolysis [3]. In addition, SCD patients who have a predisposition to allergies (atopic tendency) may also develop allergy-related bronchial asthma as well [4].

Sickle cell disease (SCD) can cause various lung function problems. Children with SCD may experience obstructive lung disease, while adults often develop restrictive lung disease and gas exchange (diffusion problems) [4].

We are conducting this study to assess the frequency of pulmonary function impairment in children with

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SCD who are routinely seen at a hematology clinic. This research aims to promote early detection and treatment to enhance health outcomes.

Methods

This cross-sectional analytic study was conducted at the Abulrish Children's Hospital on outpatients in the pediatric hematology department who were assessed by the researcher in the pediatric pulmonology department. The study was approved by the ethics committee at Cairo University, and all participants (or their guardians) provided a written consent.

We involved a group of 60 children with sickle cell disease (SCD), including those with homozygous sickle cell hemoglobin (HbSS) and those with compound heterozygous sickle beta-thalassemia (HbSβ0 and HbSβ+), both males and females from 8 years up to 18 years old in a stable state during follow-up in the hematology outpatient clinic.

Patients in sickle crises, with upper and lower respiratory tract infection within the past 2 weeks, known to have bronchial asthma, and with evidence of other chronic illness (e.g., cardiac, immunodeficiency, skeletal problems) were excluded from the study.

Procedure

A comprehensive history was obtained, with a focus on respiratory symptoms; the occurrence of dyspnea was assessed by means of the Medical Research Council dyspnea scale (MRC dyspnea scale) that measures breathlessness during exertion (i.e., grade 1: if shortness of breath with extensive exercise, grade 2: if shortness of breath only when hurrying on the level or walking up a slight hill, grade 3: if walking slower than people of equivalent age on the level because of shortness of breath or/stopping for breath when walking at the usual pace on the level, grade 4: if stopping for breath after walking for 100 yards or after several minutes on the level, and grade 5: if too breathless to go outside home [5]), the frequency of vaso-occlusive crises (VOCs), frequency of blood transfusions in the last year, and the intake of hydroxyurea. A clinical examination was carried out on all patients, along with the collection of the most up-to-date laboratory data from their records.

The patients underwent a pulmonary function test (PFT) using spirometry.

In this study, we used a set of equations (GLI equations = Global Lung Initiative equations) [6] to predict lung function (FVC, FEV1, and FEV1/FVC ratio) for participants based on characteristics like age, gender, height, and ethnicity. Then, we compared these predicted values to a standard reference value (lower limit of normal, LLN 5%) to identify participants with abnormal lung function [7].

After that, we used guidelines by the American Thoracic Society/European Respiratory Society (ATS/ERS) to categorize participants' lung function [8]. Those with an FVC less than 80% of the predicted value were classified as having a restrictive abnormality, whereas participants with an FEV1/FVC ratio below the lower limit of normal (LLN) were classified as having an obstructive abnormality. Finally, if both FVC and FEV1/FVC fell below the LLN, participants were categorized as having a mixed pattern abnormality.

Statistical methods

In this study, we utilized the IBM SPSS Statistics version 28, to manage and encode the data (IBM Corp., Armonk, NY, USA). Quantitative data were summarized using means and standard deviations, while categorical data were described using frequencies and percentages.

Group comparisons were conducted using appropriate statistical tests depending on the data distribution. Normally distributed quantitative data were analyzed with ANOVA and post hoc comparisons or the unpaired *t*-test. Non-normally distributed quantitative data were analyzed with non-parametric tests like the Mann–Whitney *U* test or the Kruskal–Wallis test. Chi-square (χ^2) tests were used to compare categorical data (Chan, 2003a).

Results

This is a cross-sectional analytic study carried out on sixty patients with SCD; 73.3% of the study population was homozygous SS, 21.6% was SB^+thalassemia (reduced B-globin chain), and 5% was SB^0 (absent B-globin chain) with a mean age of 11.4 years (±2.7 SD). Most of them were diagnosed SCD at a mean age of 36 months (±30 SD). Patients from urban cities represented 80% of the study population (Table 1).

We investigated respiratory symptoms and lung function in this population. The most common symptom was dyspnea, with varying degrees of severity according to MRC dyspnea scale. Grade 1 dyspnea was found in 15 patients (25%), grade 2 dyspnea was found in 20 patients (33.3%), and grade 3 dyspnea was found in 25 patients (41.7%). Only 4 patients (6.7%) had cough; only one among them had nocturnal cough (1.7%) (Table 2).

Spirometry measurements showed abnormal results in 28.3% ($n=17$) of the patients, with 5 patients showing an obstructive pattern (8.3%), 10 patients showing a restrictive pattern (16.7%), and 2 patients showing a combined obstructive and restrictive pattern (3.7%) (Fig. 1). They were two male homozygous SS patients who were 8 and 10 years old, on hydroxyurea, and received frequent

Table 1 Qualitative demographic data of studied sickle cell patients

		N = 60	%
Gender	**Male**	35	58.3
	Female	25	41.7
Frequency of VOCs during the last year	**Mild**	48	80.0
	Moderate	9	15.0
	Severe	3	5
Current hydroxyurea dose (mg/kg/day)	**= 15 mg**	21	35.0
	> 15 mg	33	55
History of splenectomy		5	8.3
Frequency of blood transfusion last year		42	70
Diagnosis	**SS**	44	73.3
	SB^+	13	21.6
	SB^0	3	5
Last Hb level (g/dL)	**< 10 g/dL**	40	66.7
	≥ 10 g/dL	20	33.3
Residence	**Urban**	48	80
	Rural	12	20
No. of patients on inhaled steroids (ICS)		3	5.0
No. of patients on inhaled B_2 agonists (on demand)		1	1.7

Abbreviations: *VOCs* Vaso-occlusive crises, *No.* Number, *Hb* Hemoglobin, *ICS* Inhaled corticosteroids

Table 2 Lower respiratory symptoms in studied sickle cell patients

		N = 60	%
Dyspnea	**Grade 1**	15	25.0
	Grade 2	20	33.3
	Grade 3	25	41.7
Cough		4	6.7
Nocturnal cough		1	1.7
Wheezing		3	5.0

blood transfusions. They were not statistically added in the latter tables to minimize bias.

The mean forced vital capacity (FVC) was 90.8 ± 15 SD, the mean forced expiratory volume in the 1st second (FEV1) was 89.6 ± 19 SD, and the FEV1 ratio was found to be 98.3 ± 13.3 (mean FEV25 (77 ± 39 SD), FEV50 (84.6 ± 27 SD), FEV75 (77 ± 21.9 SD)).

According to the results of the pulmonary function test (PFT), our patients were classified into 3 groups: normal group (n = 43), obstructive group (n = 5), and restrictive

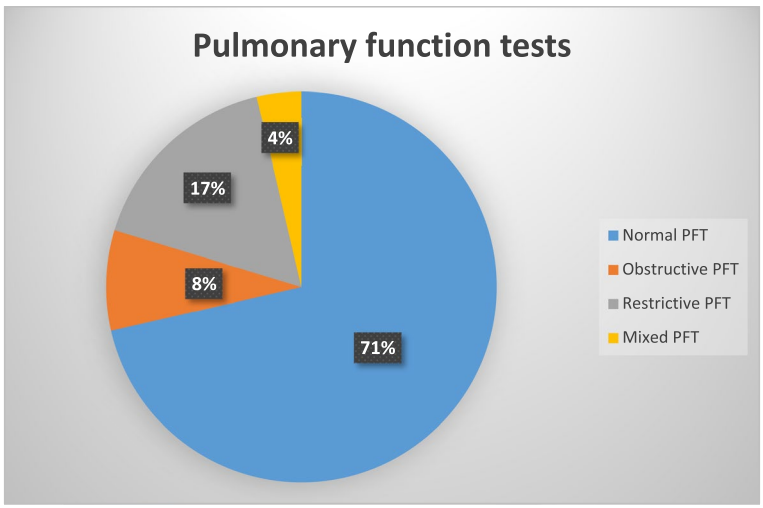

Fig. 1 SCD patient classification according to PFT

Table 3 ANOVA for clinical and laboratory data of SCD patients with normal and abnormal PFT

	Normal PFT ($n=43$)		Obstructive PFT ($n=5$)		Restrictive PFT ($n=10$)		*p* value
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	11.63	2.88	10.80	1.64	11.40	2.27	0.230
Weight *Z* score	−0.61	1.53	−1.45	0.85	−1.49	1.15	0.168
Height Z score	−0.80	1.50	−1.54	0.90	−0.91	0.71	0.437
BMI *Z* score	−0.05	1.34	−0.79	0.47	−1.47 −	1.18	0.021*
Blood transfusion frequency last year	2.74	4.09	2.00	1.22	2.00	1.33	0.086
HU dose (mg/kg/day)	15.91	9.76	20.00	7.97	24.80	6.23	0.012*
Age of start of HU	4.23	3.59	2.80	1.10	3.00	0.94	0.850
Daytime O_2 saturation %	96.28	1.10	96.40	1.52	97.00	0.67	0.214
Reticulocytic count %	1.23	0.84	1.12	0.50	1.24	0.67	0.541
Indirect bilirubin (mg/dL)	1.07	0.72	2.08	0.86	1.12	0.51	0.056
Last Hb level (g/dL)	9.51	1.40	9.30	0.55	9.04	1.46	0.927

Abbreviations: *Hb* Hemoglobin, *HU* Hydroxyurea

group ($n=10$). The comparison of the 3 groups is shown in Table 3. A statistically significant difference was found between the three groups as regards BMI *Z* score (lower in the restrictive PFT group) (p-value = 0.021) and the hydroxyurea dose (higher in the restrictive PFT group) (p-value = 0.016).

Subsequent post hoc analysis of the previous results revealed a statistically significant difference in BMI ($p=0.007$), with the restrictive group having a lower BMI compared with the normal group. The analysis also showed a statistically significant difference in HU dose ($p=0.022$), with those in the normal PFT group receiving a lower dose compared with the restrictive PFT group.

In Table 4, FEV1 was negatively correlated with hydroxyurea dose ($r=-0.34$, $p=0.007$) and blood transfusion frequency ($r=-0.27$, $p=0.031$).

Also, FVC was negatively correlated with hydroxyurea dose ($r=-0.399$, $p=0.002$), blood transfusion frequency ($r=-0.305$, $p=0.018$), and HbS level ($r=-0.277$, $p=0.032$).

Discussion

Sickle cell disease (SCD) is the most common among the inherited blood diseases, and its prevalence is rising worldwide. People with SCD often have abnormal lung function [9], which can lead to other health problems and a lower quality of life.

Our goal was to determine how common lung function problems are among young individuals with SCD. The results indicate a concerning trend that children with SCD seem to be at a higher risk for compromised lung function.

Table 4 Correlation between FEV1, FVC in SCD and clinical data

	FEV1		FVC		FEV1 ratio	
	Correlation coefficient	*p* value	Correlation coefficient	*p* value	Correlation coefficient	*p* value
Clinical data						
Hydroxyurea dose (mg/kg/day)	−0.344	0.007	−0.399	0.002	−0.02	0.866
Last Hb level (g/dL)	0.08	0.503	0.25	0.054	−0.158	0.22
Reticulocytic count%	−0.98	0.455	−0.177	0.177	−0.009	0.945
Indirect bilirubin (mg/dL)	−0.85	0.519	−0.020	0.877	−0.105	0.424
Blood transfusion frequency in the last year	−0.27	0.031	−0.305	0.018	−0.1	0.407
VOCs in the last year	−0.65	0.62	−0.159	0.226	0.088	0.504
BMI score	0.15	0.24	0.203	0.120	−0.005	0.96
Hb S level	−0.113	0.391	−0.277	0.032	0.102	0.438
Hb F level	−0.108	0.413	−0.047	0.723	0.028	0.834

Abbreviations: *FEV1* Forced expiratory volume in the 1st second, *FVC* Forced vital capacity *BMI* Body mass index, *Hb* Hemoglobin

Lung function tests using spirometry showed that nearly a third (28%) of the SCD patients in this study had impairments. This finding is supported by another study conducted on Kuwaiti children with SCD (average age 10.5 years). The study reported that 26.3% of the SCD patients evaluated exhibited problems or changes in their lung function [10].

In the current study, changes in pulmonary functions could be observed as young as 8 years old (this was the youngest age group included in our study). The obstructive pattern ($n=5$, 8.3%) was more prevalent in the younger patients (mean age = 10.8 years ± 1.6SD); however, the restrictive pattern ($n=10$, 16.7%) was generally predominant among the total study population (mean age = 11.4 ± 2.2 SD).

A comparable study on 64 children (8–15 years old) found abnormal spirometry results in 15 patients (23.4%) [11]. These results included restrictive lung disease ($n=8$, 12.5%) and obstructive lung disease ($n=7$, 10.9%). Contrarily, in another study held on Kuwaiti SCD children, with a mean age of 10.5 years, there was a predominant obstructive pattern, but this may be because the studied age group was relatively younger [10]. Airflow restriction is frequently detected in SCD children undergoing spirometry [12]. The obstructive lung finding may be caused by pulmonary vascular engorgement compressing the distal airways as well as airway remodeling and inflammation associated with vascular occlusion together with hemolysis in the pulmonary microcirculation [13, 14]. However, research on SCA in adults and adolescents reveals that a restrictive physiology emerges with aging, most likely as a result of cumulative lung damage [15].

In our study, patients showing restrictive pulmonary function test had a significantly lower BMI Z score (p-value = 0.021) when compared with those SCD with normal PFT, contrary to another study that revealed a higher prevalence of obstructive spirometry in UK-based patients with SCA (hemoglobin SS phenotype) aged 6–18 compared with their Nigerian counterparts. This finding aligns with the observation that Black African children with SCA residing in low-income settings exhibited a more frequent restrictive spirometry pattern, suggesting a disparity in lung function presentations across income levels.

A Nigerian study involving 113 adults and children with sickle cell disease (SCD) found no correlation between body mass index (BMI) and lung function [16]. However, this research also showed that SCD patients had generally lower BMIs and lung function compared with healthy individuals [17]. Importantly, over 40% of the SCD patients had abnormal lung function, with the most frequent abnormality being a restrictive pattern (almost 28%) [17]. In children with SCD, a restrictive lung function pattern suggests a potentially more serious form of chronic lung disease [16].

Research suggests that frequent bone infarctions in the spine, breastbone, and ribs can restrict chest wall growth in SCD patients. This limitation may hinder their overall development and potentially cause reduced lung capacity [16].

Patients with sickle cell disease (SCD) and restrictive lung disease received higher hydroxyurea dosages compared with those with normal lung function (p-value = 0.022). This finding suggests a possible link between higher hydroxyurea dosage and greater disease severity. It could be that patients who require higher hydroxyurea doses have a more advanced stage of the disease and experience more complications [16]. Research from high-income countries has shown that hydroxyurea use improves lung function in patients with SCD in the long term [18].

This study found a trend towards lower hemoglobin levels in the group with restrictive lung function, although this was not statistically significant. This aligns with another study on African children with SCA, which showed a link between low hemoglobin and a restrictive spirometry pattern [16].

Studying the relationship between lung functions (FEV1, FVC, FEV1/FVC ratio) and other clinical data, there was a weak positive correlation between FEV1 and body mass index (BMI) percentile ($r=0.15$, $p=0.24$), but this was not statistically significant. This is similar to another study that used a more complex statistical model and found that lung function (FEV1) improves with increasing BMI, but only up to a certain point [19]. Additionally, research by Arigliani et al. suggests that SCA patients with wasting are more likely to have restrictive spirometry patterns [16].

Furthermore, our research identified a weak negative correlation between FVC and increased levels of HbS ($r=-0.277$, $p=0.032$). This suggests a connection between HbSS severity (higher HbS) and restrictive lung disease (lower FVC). Klings et al. provide further explanation for this association [20]. Additionally, a separate Ghana study involving HbSS patients found a significantly higher risk of abnormal lung function compared with healthy individuals [21]. Therefore, HbS increases the chances of having problems with lung function and reduced lung volume.

In a previous study, Lunt et al. found that SCA patients with lower hemoglobin levels had more engorged lung capillaries together with higher resistance to airflow, suggesting a mixed pathology [22]. They proposed that blood vessel congestion in the lungs squeezed the small airways from outside, resulting in the increased resistance of the airways. It is possible a similar process is happening in

our patients. The fact that a restrictive spirometry pattern was more common might indicate more severe chronic lung damage in Egyptian children with SCA compared with those in the UK.

This study also found that lung function measurements, FEV1 and FVC, decreased as both the dosage of hydroxyurea (HU) and the frequency of blood transfusions increased. This correlation was statistically significant (p-values < 0.05). These findings contradict a previous study on 38 Kuwaiti children with sickle cell disease (SCD) that did not observe any association between lung function and HU use or blood transfusions [10]. It is important to note that the previous study had a smaller sample size ($n = 38$) and compared children with SCD to healthy controls, whereas this study focused solely on individuals with SCD.

Conclusion

Our findings suggest that lung function problems are common in children with sickle cell disease, and maintaining a high index of suspicion is important. To ensure timely identification, we recommend including an annual respiratory assessment in the routine care plan for all sickle cell disease patients.

Limitations

Our study had certain limitations, due to the small sample size relative to the disease prevalence and the lack of assessment on how comorbidities impacted patients' well-being.

Abbreviations

SCD	Sickle cell disease
PFT	Pulmonary function tests
BMI	Body mass index
GLI	Global Lung Initiative
ATS	American Thoracic Society
ERS	European Respiratory Society
FVC	Forced vital capacity
FEV1	Forced expiratory volume
VOCs	Vaso-occlusive crises
LLN	Lower limit of normal
Hb	Hemoglobin
MRC	Medical Research Council

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Authors' contributions

A.S.M.: engaged in the research design, follow-up, and supervision of all work, critical assessment of the manuscript, and final approval of the published edition. I.Y.: participated in the research design, follow-up, and supervision of all work, critical assessment of the paper, and final approval of the published edition. D.H.H.: participated in the performance and interpretation of pulmonary function tests, critical assessment of the paper, and final approval of the published edition. A.M.K.: patient recruitment, data collection, data entry, paper drafting, and review and approval of the final version. B.B.A.: revision of the manuscript and final approval of the published edition.

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Availability of data and materials

All data used in this article will be freely available to other researchers for non-commercial usage upon request to the corresponding author.

Declarations

Ethics approval and consent to participate

The ethics committee of Cairo University accepted the study procedure.
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All patients and legal guardians provided written informed consent.

Consent for publication

Written informed consent was obtained from the parents; patient data have been enrolled anonymous.

Competing interests

The authors declare that they have no competing interests.

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