IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
www.iosrphr.org Volume 4, Issue 9 (September 2014), PP. 31-37

Study of some Pulmonary Function Tests in Children with Sickle Cell Anemia: Correlation with Iron Overload

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ABSTRACT:
Background: *Sickle cell disease is hereditary hemoglobinopathy characterized by abnormal hemoglobin production, hemolytic anemia, and intermittent occlusion of small vessels, leading to acute and chronic tissue ischemia, and organ damage. Pulmonary function tests can differentiate between obstructive or restrictive lung diseases, assess the severity of the disease and evaluate the degree of efficacy of therapy in patients with sickle cell anemia.*
Objective: *The aim of this study was to study pulmonary function tests in children with sickle cell anemia and its correlation with iron overload.*
Patients and methods: *This study was carried out on 40 children with sickle cell anemia under follow up at Hematology unit, Pediatric Department, Tanta university hospital in the period between October 2012 and August 2014 including 24 males and 16 females with their age ranging from 9– 15 years and mean age value of 12.7±2.2 years and 40 healthy children as a control group including 22 males and 18 females with their age ranging from 7 – 15 years and mean age value of 10.3±2.36 years. All patients were subjected to the following investigations: Complete blood count, HB electrophoresis, serum ferritin, serum iron, total iron binding capacity and pulmonary function tests.*
Results: *There were significantly higher serum ferritin, serum iron and lower TIBC in patients than controls, significantly lower Forced vital capacity (FVC), Forced expiratory volume in one second (FEV1), FEV1/FVC ratio, Peak expiratory flow rate, and Forced expiratory Flow in patients compared with controls, significant negative correlation between serum ferritin and both of FVC and FEV1 in studied patients. There were restrictive spirometric pattern in 30 patients with sickle cell anemia (75%) and mixed obstructive and restrictive pattern in 10 patients (25%) with highly significant differences between patients and controls regarding restrictive and mixed pattern of spirometry.*
Conclusion*: Most SCD patients show abnormal pulmonary functions, predominantly of restrictive pattern.*
Recommendations: *Patients with SCD should undergo pulmonary function tests to detect and confirm lung disease for early and proper therapeutic intervention.*
KEY WORDS: *Sickle cell anemia. Iron overload. Pulmonary functions*

I. INTRODUCTION

Sickle cell disease is hereditary hemoglobinopathy characterized by abnormal hemoglobin production, hemolytic anemia, and intermittent occlusion of small blood vessels, leading to acute and chronic tissue ischemia, chronic organ damage and organ dysfunction [(1)].Hemoglobin S is the result of a single base-pair change, thymine for adenine, at the sixth codon of the β globin gene. This change encodes valine instead of glutamine in the sixth position in the β globin molecule [(2)]. Damage to the erythrocyte cell membrane occurs as it passes through the microcirculation, shortening its life span and causing a chronic hemolytic anemia [(1)]. Intravascular hemolysis produces a state of endothelial dysfunction, vascular proliferation and pro-oxidant and pro-inflammatory stress [(3)].Acute and chronic pulmonary complications occur frequently in patients with SCD, and represent the most common cause of death from SCD in adulthood [(4)]. Although the pathogenesis of chronic pulmonary disease in SCD has not been clearly defined, recurrent microvascular obstruction resulting in the development of pulmonary hypertension, endothelial dysfunction, and parenchymal fibrosis are probably the primary mechanisms [(5)].

Aim of the work

The aim of this work was to study pulmonary function tests in children with sickle cell anemia and its correlation with iron overload.

Patients and methods

This study was done after approval from ethical committee of research center in Tanta University Hospital and informed written parental consent from every case that participates in this research and was carried out on 40 children with sickle cell anemia under follow up at Hematology unit, Pediatric Department, Tanta university hospital including 24 males and 16 females with their age ranging from 9– 15 years and mean age value of 12.7±2.2 years and 40 healthy children as a control group including 22 males and 18 females with their age ranging from 7 – 15 years and mean age value of 10.3±2.36 years .

Inclusion criteria:

Patients with sickle cell anemia with age between 5 -18years.

Exclusion criteria:

Children with SCA with history of bronchial asthma or other lung diseases.
Children with sickle cell anemia of smoker parents.

All the children in both groups were subjected to the following:

1. Complete history taking.
2. Thorough clinical examination with especial account on pallor, jaundice, mongoloid facies, splenomegaly and hepatomegaly.
3. Laboratory investigations:

Specimen collection and handling:

Four ml of venous blood were collected using sterile needles through gentle venipuncture after sterilization of site of puncture by alcohol, and collected samples were divided into; 2 ml in a plain glass tube that were allowed to clot for 4 minutes and then centrifuged to separate serum which was used for estimation of serum iron, serum ferritin and TIBC [6,7], one ml was delivered on 20 uL EDTA solution for complete blood count including reticulocytic count and differential white blood cells count which was done on Leishman stained peripheral blood smear with evaluation using ERMA PCE-210 N cell –counter [8] and one ml was added to 2 ml hemolysate for Hb electrophoresis [9].

Pulmonary function tests:

Pulmonary functions were measured by the aid of a Flow-volume Spirometry Using 1999 ZAN Messgeraete Gmbh Germany. Pulmonary function device is completely automated which run on computer system. The computer is running CAP (computer aided pulmonary diagnostic software) consists of programs for measuring pulmonary functions. The computer programs uses the data (age, height and weight) of examinee to determine the values of parameter expected and actual expressed in percentage. No child with SCA was tested within 2 weeks of an upper respiratory tract infection and within 1 month of vaso-occlusive crisis [10]. The following parameters have been measured using spirometry; Forced vital capacity (FVC), Forced expiratory volume in one second (FEV1), FEV1/ FVC ratio, Peak expiratory flow rate (PEFR) and Forced expiratory flow (FEF) [11].

Statistical Analysis

Data were collected and analyzed using statistical package for social science (SPSS) version for windows (version 12). All Data were expressed as in terms of mean values ± SD. Comparisons of parameters among groups were made using the paired t test. Two-group comparisons were performed nonparametrically using the Mann-Whitney U test. All statistical tests were two tailed, and $P < 0.05$ was considered statistically significant.

II. RESULTS

[1].There were no statistically significant differences between patients and controls as regards age and sex but there were statistically significant differences as regards pallor, Jaundice, hepatomegaly and splenomegaly or splenectomy. None of controls had pallor, Jaundice, hepatomegaly and splenomegaly or splenectomy (Table I).

[2].There was significantly lower hemoglobin and significantly higher reticulocytes %, leucocytic and platelets counts in patients compared with controls (Table II).

[3].There were significantly higher serum ferritin and serum iron and significantly lower TIBC levels in patients compared with control group (Table III).

[4].There were significantly lower FVC, FVC%, FEV1, FEV1%, FEV1/FVC ratio, PEFR, PEFR% and FEF in patients compared with control group (Table IV).

[5].There was significant negative correlation between serum ferritin and both of FVC and FEV in studied patients (Figure I and table V).

[6].There were restrictive pattern of Spirometry in 30 patients with sickle cell anemia (75%) and mixed obstructive and restrictive pattern in 10 patients (25%) with highly significant differences between patients and control group regarding restrictive and mixed pattern of Spirometry (Table VI).

Table (I): Clinical data of the studied patients group.

Clinical data	(No=40) (%)
Pallor	30 (75)
Jaundice	28 (70)
Hepatomegaly	16 (40)
Splenomegaly	30 (75)
Splenectomy	10(25)
Acute chest syndrome	4 (10)
Leg ulcers	4 (10)
Sickle cell crisis	20 (50)

Table (II): Comparison of complete blood picture between patients and control group.

Parameters		Patients (no=40)	Control group (no=40)	P. value
Hemoglobin (gram/dl)	**Range**	4.1-10.3	11-13.5	0.001*
	Mean ± SD	8.01 ± 1.22	12.25 ± 0.755	
Red blood cells (million /mm^3)	**Range**	1.96-6.4	2.22-5.90	0.008*
	Mean ± SD	3.19 ± 0.89	3.76± 0.92	
Mean corpuscular volume (fl)	**Range**	73-99	74.5-100	0.65
	Mean ± SD	86.9±11.1	85.62±6.85	
Mean corpuscular hemoglobin (Pico gram)	**Range**	26-30	27-33	0.70
	Mean ± SD	28.2±1.62	29.61.5± 1.68	
Platelets (thousands/mm^3)	**Range**	160-688	150-430	0.03*
	Mean ± SD	359.6 ± 32.45	292± 18.75	
Total leucocytic count (thousands/mm^3)	**Range**	8-20	8 - 12	0.001*
	Mean ± SD	14.9± 3.291	9.95± 1.395	
Reticulocytes %	**Range**	1.8- 9	0.5 - 1.1	0.001*
	Mean ± SD	4.8± 1.98	1.63± 0.79	

*P <0.01: Highly significant, P<0.05: Significant P>0.05: non-significant

Table (III): Comparison between studied patients and control group regarding iron status.

Parameters	Patients (No= 40)	Control (No=40)	P value
Ferritin (Nano gram/ml) **Range** **Mean ± SD**	 370-4225 1665.2±1387.65	 35-335 192.55±107.2	 0.00*
Iron (Microgram/dl) **Range** **Mean ± SD**	 128-312 233.25±50.57	 60-140 120±16.57	 0.00*
Iron binding capacity (Microgram/dl) **Range** **Mean ± SD**	 174-233 203.25±18.02	 275-366 327.8.7±21.96	 0.00*

*P<0.01: Highly significant.

Table (IV): Comparison of pulmonary function tests between patients and control group

Parameters	Patients (No =40)	Control (No =40)	P value
FVC **Range** **Mean ± SD**	 0.45-3.51 1.91±0.87	 2.15-2.86 2.45±0.2	 0.011*
FVC% **Range** **Mean ± SD**	 15-71 54.4 ± 13.01	 85-99 93.5±3.8	 0.001*
FEV1 **Range** **Mean ± SD**	 0.44-1.89 1.43 ± 0.43	 1.86-2. 94 2.2 ± 0.33	 0.001*
FEV1% **Range** **Mean ± SD**	 16-58 47.1±10.86	 87-112 93.3±5.43	 0.001*
FEV1/FVC (%) **Range** **Mean ± SD**	 54-126 74.3±21.38	 77.3-108.08 89.46 ±9.06	 0.005*
PEFR **Range** **Mean ± SD**	 0.68-3.85 1.73±0.84	 3.39-5.47 4.44±0.45	 0.001*
PEFR% **Range** **Mean ± SD**	 13-63 26.9 ±14.1	 87-100 92.5 ±4.27	 0.001*
FEF **Range** **Mean ± SD**	 0.51-2.71 1.21±0.53	 3.1-4.2 3.74±0.36	 0.001*

*P <0.01: Highly significant, P<0.05: Significant P>0.05: non-significant. FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, FEV1/FVC (%): ratio of Forced expiratory volume in one second/Forced vital capacity, PEFR: Peak expiratory flow rate, FEF: Forced expiratory Flow.

Table (V): Correlation between Serum ferritin and pulmonary function tests of studied patients.

Parameters	r	P
Forced vital capacity	0.505	0.023*
Forced expiratory volume in one second	0.858	<0.001*
Forced expiratory volume in one second/Forced vital capacity (%)	-0.468	0.037*
Peak expiratory flow rate	-0.166	0.483
Forced expiratory Flow	-0.081	0.733

*P <0.01: Highly significant, P<0.05: Significant, P>0.05: non-Significant.

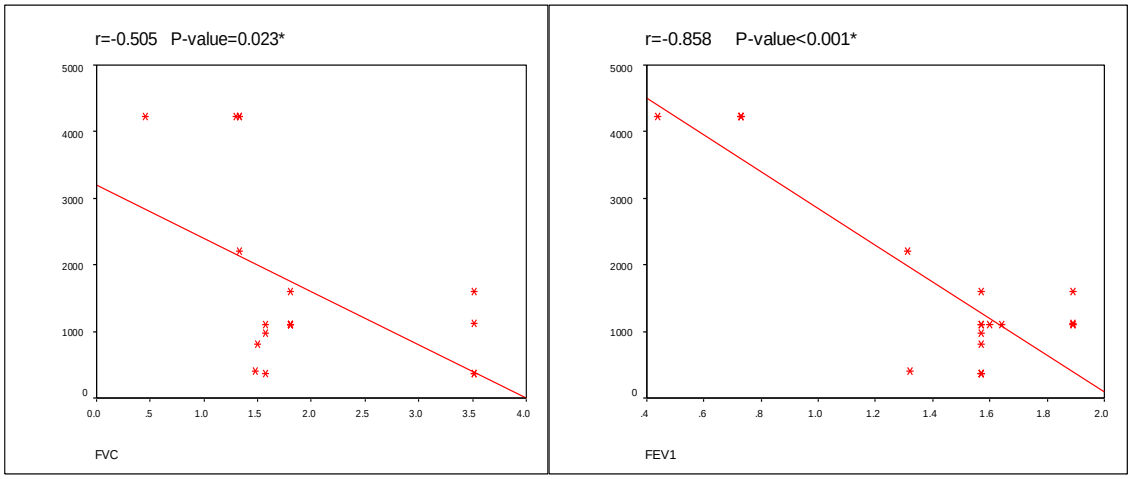

Fig (1): Correlation between serum ferritin and FVC (to the left) and between serum ferritin and FEV1 (to the right).

Table (VI): Spirometric patterns in studied patients and control group.

Pattern of Spirometry		Patients (Number =40)	Controls (Number =40)
Normal		-	40 (100%)
Restrictive pattern		30 (75%)	-
Mixed		105 (25%)	-
Total		40 (100%)	40 (100%)
Chi-square	**X^2**	40	
	P-Value	<0.001*	

* Significant

III. DISCUSSION

Sickle hemoglobin is one of the most common and clinically significant structural abnormalities of hemoglobin, but no contemporary estimates exist of the global populations affected. Moreover, the precision of available national estimates of heterozygous (AS) and homozygous (SS) is unknown [(12).] In the present study we evaluated pulmonary function tests in 40 patients with sickle cell anemia who were under follow up in the Hematology Unit, Pediatric Department, Tanta University Hospital, compared to 40 healthy individuals of same age and sex as control group.

In the current study hepatomegaly was found in 40% of SCA patients. This is in agreement with **Olaniyi and Abjah 2007** [13] who found hepatomegaly in 59% but this is not in agreement with **Sadarangani et al., 2009** [14] who found hepatomegaly in 20% and **Gurkan et al., 2005** [15] who found hepatomegaly in all patients with HbSS and concluded that liver involvement may occur due to primary disease itself or secondary conditions as iron overload, viral hepatitis and cholelithiasis. In this study, splenomegaly was found in 75% of patients and surgical splenectomy in 25% of patients with SCA however **Ballas et al., 2010** [16] reported that autosplenectomy is a common finding in patients with SCD resulting from multiple splenic infarctions with decrease in size and function.

In the present work, there was significantly lower hemoglobin level and higher reticulocytic count in patients compared with control group. This was in concordance with **McPherson et al., 2011** [17] who found same results and explained it by the nature of the disease as chronic hemolytic anemia and there was significantly higher leucocytic and platelets counts in patients compared with controls which was in agreement with **Rossef 2009** [18] who found the same results and explained this by bone marrow over production and **Ballas et al., 2012** [19] who found thrombocytosis in patients with HbSS; which could be due to process of autosplenectomy as most of children with SCA may have total loss of functional splenic tissue by early childhood.

In this current study there was significantly higher serum ferritin, serum iron and significantly lower TIBC in patients compared with controls. This was in agreement with **Akodu et al., 2013** [20] who found the same results but not in agreement with **Rodrigues et al 2011**[21] who performed retrospective study in 135 infants with SCD below 2 years old and found significantly lower ferritin and transferrin in infants with sickle cell anemia and **Kassim et al 2012**[22] who studied iron status in 75 Yemeni patients aged 1–30 years with homozygous SCD including 44 had never been transfused and 31 patients had received blood transfusions but not during the 3-months period prior to the study and found 10 patients with iron deficiency (13.3%), 9 of whom were non-transfused and they recommended to screen non-transfused SCD patients for iron deficiency.

In the present study there was significantly lower FVC and FEV1 in patients compared with control group. This was in agreement with **Sylvester et al., 2004** [23] who showed that children with SCD had significantly lower FEV1 and FVC than controls matched for sex, race and height.

In this study there was significant negative correlation between serum ferritin, FVC and FEV1 in SCA patients. This was in disagreement with **Keikhaei et al., 2011**[24] who reported no significant correlation between serum ferritin, FVC, FEV1, FEF and FEV1/FVC in SCD patients. In the present work, there were restrictive spirometric pattern in 75% of studied patients with sickle cell anemia and mixed obstructive and restrictive pattern in 25% of patients which was consistent with **Klings et al 2006** [25]**, Elizabeth**, **2008** [26] and **Hulke and Thakare, 2011**[27] who found the same results but not in agreement with **Arteta M et al 2014** [28] who studied 146 children aged 7-20 years with hemoglobin SS or Sβ-thalassemia and found that 80% of the patients had obstructive physiology, 9% had restrictive physiology and 11% had abnormal but not categorized physiology.

Variation between our study and previous studies may be explained by different locality, different number of studied patients, variations in ages of studied patients, variations in severity of disease, variations in degree of iron overload and compliance with iron chelating agents. The restrictive pattern may be attributed to lung injury resulting from repeated episodes of pulmonary damage as acute chest syndrome, pneumonia, fat embolization, and pulmonary hypertension [29]**.** It can also result from ineffective inspiration caused by pain and structural impairment of the chest as a consequence of rib infarction during bone growth, vertebral osteoporosis or osteomalacia [30].

IV. CONCLUSION

Pulmonary function tests differ significantly in patients with SCA compared with controls of matched age and sex. Most SCD patients presented with abnormal pulmonary functions, being predominant of restrictive pattern. **Recommendations:** Patients with SCD should undergo pulmonary function tests using Spirometry as pulmonary function tests appear to be the first tests to show abnormalities during the course of the lung disease and sensitive to detect and confirm lung disease.

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