

Clinical Expression of Homozygous Sickle Cell gene in Yemeni Children

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Abstract

In this study the demographic and clinical profile of 105 Yemeni children under 16 years old with sickle cell anemia (SCA) were studied. They were 53 males (50.4%) and 52 females (49.5%), aged between 0.5 and 15 years (mean 7.4ys). The most serious crisis as vaso-occlusive, hemolytic, sequestration and aplastic crisis were seen in (83.8%), (52.3%), (6.6%) and (5.7 %) respectively. The hand-foot syndrome was found in (21%) of all patients and in (51%) of children less than 3 years old. The most serious complication was the respiratory tract infections which was the most frequent in these patients, being encountered in (65.7%). The rate of hospitalization was of (76%). Our findings show that SCA has a severe clinical course in Yemenis, resembling that in black Africans and in black Americans.

Keywords: Sickle cell severity, Yemen, HPLC.

(J Med J 2013; Vol. 47 (4):340-347)

Received

July 31, 2012

Accepted

August 6, 2013

Introduction

Sickle cell anemia (SCA) is a hereditary and chronic hemolytic anemia characterized by varying degree of hemolysis and intermittent episodes of vascular occlusion. Hemoglobin S (HbS) in its reduced form [deoxy-hemoglobin S] precipitates and forming polymers within the red blood cells causing deformation of their membrane which take the characteristic form of sickle red blood cells. This property of HbS is the result of a point mutation in which a single nucleotide in the 6th position of the β globin gene is replaced with another nucleotide that led to replacement of glutamic acid in the 6th position of the β globin chain by a molecule of valine (β^S 6 GLU. \rightarrow .VAL)^(1, 2).

SCA is prevalent through many parts of the world particularly where the malaria, caused by plasmodium falciparum, is highly endemic such as in tropical Africa, Middle East, Mediterranean countries, Arabian Peninsula and parts of India. The population migrations have ensured that it is now encountered in Europe and America⁽¹⁾.

SCA is characterized by periods of remissions and exacerbations called crises. Its manifestations include chronic and acute hemolytic anemia with frequent blood transfusion requirements, vaso-occlusive crisis and a great susceptibility to infection⁽³⁾. The anemia in SCA patients is complicated by other crisis such as: aplastic crisis, acute sequestration in spleen and hyper- hemolytic

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crisis⁽⁴⁾. Despite the unicity of the genetic mutation that is responsible, the clinical expression of HbS is reported to be variable according to regions and even within the same population. It ranges from a severe disease with painful crisis and life threatening complications to a disease with mild symptoms. The heterogeneity of the phenotypic presentations were linked to the differences among haplotypes of beta globin gene^(5,6).

Few studies have been published from Yemen on SCA .This study ,however ,is the first study dealing with clinical presentation of SCA from Taiz governorate which is located in the south-western region of Yemen with population of about 2.5 millions⁽⁷⁾.

The purpose of this study is to evaluate the

demographic and clinical profile of SCA in Yemeni children from Taiz governorate and to compare our results with the results published in the literature.

Patients

Our study includes one hundred and five children under 16 years old, attended the martyr Mohamad Al-Dura clinical center for blood diseases in Taiz during the period June 2007 - June 2008.The age range was between 0.5 - 15 years old with a mean age of 7.4 years. Distribution of the patients according to age groups and sex is shown in table (1). The diagnosis of SCA was done by clinical presentation suggesting SCA and confirmed by laboratory tests as mentioned in the methods. Cases of SCA associated with β or α -thalassemia were excluded from this study.

Table 1. Age and sex distribution of 105 Yemeni children with SCA from Taiz-Yemen

Gender	1-5		6-10		11-15		Total	
	N	%	N	%	N	%	N	%
Male	23	15.7	17	11.6	13	8.9	53	50.4
Female	20	13.6	16	10.9	16	10.9	52	49.6
Total	43	29.4	33	22.6	29	19.8	105	100

Methods

On every patient physical examination was carried out, Personal and family history was taken including the history of the extent of previous hospitalizations and the number of blood transfusions received in the past .Chest X-ray and Abdominal sonography were done to all patients under evaluation .All data were filled in standard forms .Five milliliters of blood was drawn into EDTA tubes. Sickling test was used for sickle screening. The blood smears were prepared and air dried and the red

cell morphology was studied after staining with Giemsa stain⁽⁸⁾.The whole blood was used for the estimation of hematological parameters on Coulter Counter SYSMEX JAPAN. The red cell indices were obtained from the Coulter Counter⁽⁸⁾. The hemoglobin electrophoresis was carried out in all sickle cells positive samples using Helena TITAN III instruments on cellulose acetate plate in alkaline buffer⁽⁸⁾.Confirmation of the presence of hemoglobin S and quantification of Hemoglobin S, A2 and F were done by BIO-RAD D10 instruments using the method of

high pressure Liquid chromatography (HPLC)⁽⁸⁾.

Results

The patients had around equal sex distribution. They were 53 males [50.4%] and 52 females [49.6%] as seen in table (2). Twenty one of patients were children under 3 years of age (20.9%).Sixteen patients (15.2 %) lived In Taiz city and 89 patients (84.7 %) came from different rural regions of Taiz governorate. Sixty patients (57.1%] had positive family history of sickle cell disease, with one affected family member in (34.3 %), two affected family members in (16.1%) and three affected family members in (6.6%) of patients.

At the time of diagnosis, the hemoglobin level of less than 6 gm/dl was found in 17 patients (16.1 %), a level between 6 to 9 gm/dl in 72 patients (68.5%), and between 9 and 12 gm/dl was found in 16 patients (15.2%). The mean hemoglobin was 7.3 g/dl and the mean percentage of HbS was 75.6% as seen in table (2). About 76% of cases (80 patients) were

hospitalized. Forty four patients (41.5 %) had been hospitalized twice to four times per year. Eighty patients (76.1%) received blood transfusion of whom (46.6 %) were transfused more than three times per year. Vaso-occlusive crisis occurred in 88 patients (83.8%) of whom 78 patients (74.2%) had joints and bones pain; 65 patients (61.9%) had back pain; 44 patients (42.3%] had chest pain; 43 patients (40.9%) had abdominal pain .The Hand-foot syndrome was seen mainly in half of the children under 3 years of age, and in 22% of all patients studied. Acute sequestration crisis was seen in 7 patients (6.6 %); all of them were below 7 years. The aplastic crisis was diagnosed in 6 patients (5.7%). Hyper hemolytic crisis occurred in 55 patients (52.3%). Severe pneumonia that required hospitalization had been registered in 29 patients (27.6%). Meanwhile, upper respiratory tract infection was diagnosed in 69 patients (65.7%). Malaria parasites were seen in the peripheral blood films of 27 patients (25%). Biliary stones were seen in 4 children (3.8%). Table (3) shows the major clinical presentation of our cases with SCA from Taiz.

Table 2. Level of hemoglobin with it's different types in 105 children with SCA

Variable	N=105	Mean	Min	Median	Max
Hb g/dl	105	7.3	2.9.	7.5	11.1
HbS%	105	76.50	42.00	80.00	95.00
HbF%	105	11.23	1.0	10.00	28.00
HbA2%	105	3.72	0.900	3.80	5.40

Table 3. Clinical presentation in 105 Yemeni children with SCA from Taiz

Clinical Manifestations	Number of patients	%
Pain crisis	88	83.3
Anemia	87	82.9
Transfusion	80	76.2
Bone and Joint pain	78	74.3

Clinical Manifestations	Number of patients	%
Fever	70	66.7
Upper respiratory tract infections	69	65.7
Back pain	65	61.9
Jaundice	57	54.3
Splenomegaly	48	45.7
Chest pain	44	41.9
Abdominal pain	43	41
Hepatomegaly	40	38.1
Joint swelling	31	29.5
Pneumonia	29	27.6
Malaria	27	25
Hand foot syndrome	22	20.9

Discussion

In Yemen HbS gene has been reported to occur in several regions of the country. The prevalence of sickle cell gene in patients originated from Taiz governorate was reported to be the highest and is around 8.2%⁽⁹⁾. The clinical manifestations of the sickle cell anemia in Yemenis was shown to be sever resembling the disease severity in black Africans as reported by Alsaqlady et al., and El hazmy et al.,^(10,11).

All the patients included were diagnosed on clinical presentation suggesting SCA and latter on was confirmed by laboratory tests. Twenty one percent of our patients were diagnosed before the age of 3 years and this may reflect the disease severity in early life. The morbidity of SCA can be estimated from the frequency of the major clinical presentations of the SCA which include: painful crisis due to vaso-occlusive events, hemolytic crisis and hand - foot syndrome (in early childhood) and frequency of patient's hospitalization and blood transfusion given ^(3,4,5, 12).

The hospitalization rate of (76%) in this study is similar to (77%) reported from Oman⁽¹³⁾ and is higher than (20%) reported from Eastern Saudi Arabia⁽¹⁴⁾. Painful crisis was the commonest cause of hospitalization in our patients (83.8%) which is a very high rate, compared to the rates reported in Yemeni children from Aden (70%)⁽¹⁰⁾, Eastern Saudi Arabia (21%)⁽¹⁴⁾, Jamaica (18 %)⁽¹⁵⁾, and south London (35%)⁽¹⁶⁾. The rate reported from Oman (90%) was higher than our rate⁽¹³⁾. The incidence of hand foot syndrome was found in (51.2 %) of our children under 3 years of age. This rate is similar to (54%) reported from Yemeni children from Aden⁽¹⁰⁾. However, it wa higher than (43%), (14%) and (40%) reported from Oman⁽¹³⁾ Eastern Saudi Arabia⁽¹⁴⁾ and Jamaica⁽¹⁵⁾ respectively. This may be considered as an evidence of increased disease severity in our patients.

Abdominal crisis occurred in (41.1%) of our cases which is lower than (80 %) reported in Omani cases ⁽¹³⁾, but It was higher than (5%) and (18%) reported from Eastern Saudi Arabia and Jamaica respectively ^(14, 15). These different rates are example of variable clinical

manifestations in different populations. Table (4) shows the clinical presentation in our SCA

children and those from Aden, Oman, Saudi Arabia and Jamaica.

Table 4. Major Clinical presentation of Yemeni children with SCA from Taiz Yemen as compared to other studies

parameter	Taiz Yemen %	Aden Yemen %	OMAN %	East Saudi Arabia %	Jamaica %
Painful crisis	83.8	70	90	21	18
Hand and foot syndrome	51.1	54	43	14	40
Abdominal crisis	41	-	80	5	18
Splenic Sequestration crisis	6.6	-	7	1	25
Aplastic crisis	5.7	-	2	2	9
Hemolytic crisis	52.3	16	59	2	-
splenomegaly	45.7	40	38	33	80
Hepatomegaly	38.1	72	24	21	-

In Nigeria, hemolytic crisis in SCA children was reported to be the major cause of morbidity, mortality and hospital admission⁽⁵⁾. Anemia in those children was complicated by hyper-hemolytic, sequestration and aplastic crisis and 90% of all children under study were severely anemic.

Anemia was present in 87 patients (82.9%) of our cases. The incidence of hyper-hemolytic crisis in our children was (52.3%). This rate is higher than (16%) reported from Aden Yemen⁽¹⁰⁾ and (2%) from Eastern Saudi Arabia⁽¹⁴⁾, but is less than (59%) reported from Oman⁽¹³⁾. The association of SCA and G6PD deficiency was found in (32%) of Omani children⁽¹³⁾ which could, to some extent, explain the increased rate of hyper-hemolytic crisis in those children. The status of G6PD in our patients was not evaluated. Further study is required to investigate the possibility of co-existence of G6PD deficiency in causing hyper-hemolytic crisis in SCA Yemeni patients. Hence, the malaria infection is endemic in Yemen⁽¹⁷⁾. Another explanation of the increased hemolytic crisis rate in our children is perhaps due to

malaria infection which was found in blood films of (25%) of them. The malaria impact on clinical presentation and complications of SCA is unknown in our patients, and this may be a good subject for future research in Yemen. In Nigeria, malarial parasites were seen in the blood films of some SCA children, and has been particularly implicated as causing hyper-hemolysis in those children⁽⁵⁾.

Splenomegaly was common presentation in this study (45.7%) and this, in some patients, may progress to rapid blood sequestration in spleen causing acute splenic sequestration. Splenic sequestration crisis occurred in (6.6%) of our patients as compared to (7%) in Omanis⁽¹³⁾, (1%) in Eastern Saudi Arabia and (2.2%) in South Western Saudi Arabia^(14,18). All these rates are much lower than the reported rate of (25%) from Jamaica⁽¹⁵⁾ as seen in table -4. The incidence of aplastic crisis was (5.7%) in our cases which is more than that reported in Omanis (2%)⁽¹³⁾, and Eastern Saudi Arabia (2 %)⁽¹⁴⁾ but markedly lower than the incidence reported from Jamaica (9%)⁽¹⁵⁾.

Splenomegaly was palpable in (45.7 %) of our children, compared to (40%), (38%), (33%) and (80%) reported from Aden⁽¹⁰⁾, Oman⁽¹³⁾, eastern areas of Saudi Arabia⁽¹⁴⁾ and Jamaica⁽¹⁵⁾ respectively. Meanwhile, hepatomegaly was palpable in (38.1%) of our children which is lower than (72 %) reported from Aden⁽¹⁰⁾, and higher than (24%), (21%) reported in Omanis⁽¹³⁾ and Saudi children from eastern provinces⁽¹⁴⁾. The most frequent reported infection in our patients was the infection of the upper respiratory tract (65.7%), followed by pneumonia (27.6%).

Blood transfusion as therapy and prophylaxis in SCA should be given only in absolute necessity. Its indications include: hyper-hemolytic crisis, splenic sequestration, aplastic crisis, fulminant infection, and elective or emergency surgery⁽¹⁹⁾.

Actually, most of these complications were reported in our patients as seen in table (4). This explains the high rate of blood transfusion given to (76.6%) of our cases compared to (42.9%) in Saudi patients from eastern provinces⁽¹²⁾, and the (45%) in Omani patients⁽¹³⁾. Another explanation for this high rate in Yemeni SCA children compared to others, might be due to the difference in hospital policy in different countries for anemia correction.

The previous discussed findings indicate the severity of SCA in Yemeni children and also show the variable clinical presentation in

different ethnic groups as shown in table (4). Furthermore, Our findings highlight the nature of the SCA in Yemenis. In fact, they are in concordance with the previous studies which showed that the Yemeni SCA haplotype is of African origin which is characterized by a sever course of disease^(9,10,11).

Conclusion

This is the first study on sickle cell anemia in Yemeni children from TAIZ governorate. Although the study represents the governorate of Taiz, it highlights the severity of SCA in Yemeni patients, resembling the black Africans or black Americans. These similarities between Yemenis and Africans regarding the SCA haplotype and the clinical presentation might be due to the intermarriage of Africans with Yemenis who emigrated and lived in Africa for several generations. Then, they returned to Yemen after the political and economical instability in African countries as well as the geographical neighborhood between the two nations.

Recommendations

Further population -based studies are required to build a solid scientific data which will help in creating a national registry of Hemoglobinopathies, thalassemia and enzymopathies in Yemen. In addition, studies about the malaria impact on the severity of SCD in Yemen will help in the treatment of SCA.

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الأعراض السريرية التي يعاني منها الأطفال اليمينيون المصابون بفقر الدم المنجلي

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الملخص

تمت دراسته العوامل الديموغرافية والأعراض الإكلينيكية في 105 أطفال يمينيين منهم 53 ذكرا (50.4%) و52 انثى (49.6%)، وتراوح أعمارهم بين 6 أشهر و15 عاما، ومتوسط العمر لديهم 7.4 سنة. وقد بينت الدراسة ان هؤلاء المرضى عانوا من النوبات الإكلينيكية المصاحبة لمرض فقر الدم المنجلي، مثل: النوب المسدة للأوعية الدموية، ونوب زيادة تحلل الدم ونوب تكدس الدم في الطحال، ونوب قلة إنتاج نخاع العظم بنسب: 83.3%، 52.3%، 6.6%، 5.7%، على التوالي. أما متلازمة اليد والقدم، فقد تم رصدها في 21% من مجموع المرضى تحت الدراسة، و51% من مجموع المرضى تحت سن ثلاث سنوات. وتبين أن إصابة الجهاز التنفسي العلوي بالأخماج كانت من اهم المضاعفات في 65.7% من المرضى، وأن 76% من المرضى تم إدخالهم الي المستشفيات.

وقد خلصت الدراسة إلى أن الصورة الإكلينيكية لدى الاطفال المصابين بمرض فقر الدم المنجلي في تعز ذات طابع خبيث، وتشبه الصورة الإكلينيكية لدى المصابين بمرض فقر الدم المنجلي في إفريقيا وأمريكا.

الكلمات الدالة: حدة فقر الدم المنجلي، الأعراض السريرية، الأطفال اليمينيون.