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# Features of sickle-cell disease in Bahrain

*Sheikha Salim Al Arrayed1 and Neva Haites*

## ملامح مرض الكريات المنجلية في البحرين

شيخة سالم العريض، ونيفا هايتس

تنتشر في البحرين اضرابات الهيموغلوبين الوراثية. ولقد أجرينا دراسة على مجموعة تبلغ 56198 موطناً بحرينياً يقيمون في نطاق المستشفي، ووجدنا أن 2% من المواليد مصابون بمرض الكريات المنجلية، وأن 18% منهم لديه الخّلة المنجلية، بينما كان 24% يحملون جينات التلاسيمية الألفا. ولدى دراسة طبيعة مرض الكريات المنجلية بين البحرينيين تبين لنا أن الشكل الخفيف من المرض هو الغالب، وإن كانت هناك اختلافات سريرية واسعة النطاق. كما وجدنا أن قَيم الدمويات فيهم مماثلة لتلك التي لدى مرضى المنطقة الشرقية بالمملكة العربية السعودية، حيث يغلب انتشار الشكل الخفيف من المرض.

Genetic disorders of haemoglobin are prevalent in Bahrain. In a study of the hospital population covering 56 198 Bahrainis, we found that 2% of newborns have sickle-cell disease (SCD) and 18% have sickle-cell trait, while 24% are carriers of the α-thalassaemia gene. In a study of the presentation of SCD among Bahrainis it was found that the mild form of the disease predominates, but a wide clinical variability is apparent. It was also found that their haematological values are similar to those of patients from Eastern Province, Saudi Arabia, where the mild form of the disease predominates.

## Introduction

The state of Bahrain is an archipelago of 33 islands, with the kingdom of Saudi Arabia to the west and Qatar to the east. The 1991 population was 500 000, one third non-Bahraini. Falciparum malaria was endemic in Bahrain until 1970 and so the malaria-associated genetic defects of red cells (sickle-cell disease [SCD], thalassaemia and glucose 6 phosphate dehydrogenase deficiency) were found to be common [1].

In 1990 it was found that hereditary anaemias were the third most frequent diagnosis at the Salmaniya Medical Centre, which is the main hospital in the country [1].

Sickle-cell disease (SCD) drains a country's health resources and dramatically affects family and personal life. Accordingly we decided to study sickle-cell disease among Bahrainis.

The aims of these studies were to:

1. ascertain the incidence of genetic disorders of haemoglobin in the hospital population in Bahrain
2. ascertain the natural history of sickle-cell disease among Bahrainis
3. investigate the haematological characteristics of the Bahraini SCD patient
4. identify the haplotype associated with SCD mutation among Bahrainis.

We present here a summary of four studies performed on sickle-cell disease among our population.

### 1. Prevalence of genetic disorders of haemoglobins in the hospital population of Bahrain

Blood samples of 56 198 Bahraini nationals were analysed over a six-year period (1982-1987). Of the total, 5 503 were neonatal samples (see Table 1) and the rest non-neonatal. Abnormal haemoglobin was detected in 44.35% of neonatal samples (24.2% were α-thalassaemia cases, 18.1% showed sickle-cell trait [SCT] and 2.1% had SCD). Hb Barts was the most common abnormal haemoglobin seen

| Table 1 Incidence distribution of haemoglobin patterns among cases | | |
|---|---|---|
| Hb pattern | Number of Cases | Percent |
| Hb A/F<br>Normal pattern | 3062 | 55.6 |
| Hb A/S/F<br>Sickle cell trait | 995 | 18.1 |
| Hb A/F/Barts<br>α−thalassaemia | 863 | 15.7 |
| Hb S/F/ Barts<br>Sickle cell disease with α−thalassaemia | 85 | 1.5 |
| Hb A/S/F/Barts<br>Sickle cell trait with α−thalassaemia | 384 | 7.0 |
| Total | 5503 | 100.0 |

In the non-neonatal cases, the overall frequency of SCD was found to be 10.44%, and the frequency of those with SCD and Hb F present was 8.75%, which means that nearly 84 % of the SCD patients had Hb F present. Table 2 shows the distribution of quantitation of fetal haemoglobin (Hb F) in SCD patients with Hb S/F. Hb F varied between 2% and 40%. The majority of cases (about 76%) had Hb F in the range between 4.1% and 20%. The favourable protective role played by Hb F in sickle-cell disease is well-recognized by several workers [2-8], with the severity of the disease being inversely proportional to the quantity of Hb F.
The high incidence among the non-neonatal cases is due to the fact that a good number of cases were referred for Hb electrophoresis from outpatient clinics and hospital wards, and from health centres after getting positive results from a sickling test.

| Table 2 Distribution of haemoglobin F in sickle-cell disease samples of Hb S/F among non-neonatal cases | | |
|---|---|---|
| Percentage rang of Hb F levels | Number of Cases | Percent |
| 2.0 to 4.0 | 876 | 19.55 |
| 4.1 to 10.0 | 199.0 | 45.39 |
| 10.1 to 20.0 | 1354 | 30.89 |
| 20.1 to 40.0 | 863 | 15.7 |
| total | 4384 | 100.0 |

**2. The nature of sickle-cell disease in Bahrain**

Sickle-cell disease in Bahrain and Saudi Arabia presents special features. SCD in this area is haematologically and clinically mild, and mortality is low in both children and adults [9] This benign picture results in part from very high levels of fetal Hb in the community and also from a high prevalence of a-thalassaemia. However in this environment clinical variability is apparent, with some cases dying from septicaemia and serious morbidity resulting from salmonella osteomyelitis.
This study was conducted with a view to ascertaining the nature of SCD in the Bahraini population, helping us to formulate certain palliative and corrective measures. The study was community based; a questionnaire was sent to and completed by 100 school children aged between 8 and 12 and their parents.

From this study we found that the most frequent factor cited as precipitating a crisis was exposure to cold (45% of cases). Other factors included fever or elevated body temperature (35%), exhaustion and severe physical activity (35%), hot humid weather (10%), stuffy and crowded places (10%) [10,11] (Table 3).

Table 3 Factors precipitating crisis in SCD patient

| Factors | Percent |
|---|---|
| Cold | 45 |
| Fever | 35 |
| Exhaustion, physical activity | 35 |
| Change in temperature | 19 |
| Hot weather | 10 |
| Closed crowded places | 10 |
| Mental and physiological tension | 10 |
| Vomiting, diarrhea | 7 |
| Traveling by air | 1 |

Regarding the clinical picture, fever was mentioned as the most frequent symptom (69% of responders). Other symptoms mentioned were pain in the hands (59%), pain in the limbs (58%), abdominal pain (56%) and pain in the knees (55%). Of the
sample, 36% had chest pain and only 18% had urinary problems (Table 4).

Table 4 Common signs and symptoms in Bahraini SCD patients

| Symptom | Percent |
|---|---|
| Fever | 69 |
| Pain in hands | 59 |
| Limb pain | 58 |
| Abdominal pain | 56 |
| Knee pain | 55 |
| Back pain | 54 |
| Elbow pain | 40 |
| Shoulder pain | 39 |
| Chest pain | 36 |
| Urinary problem | 18 |
| Myopia | 12 |
| Gall stone | 1 |

Almost 55% of respondents mention fava beans as a precipitating cause of a crisis. Although not documented, an explanation for this may be the high incidence of glucose 6 phosphate dehydrogenase (G6PD) deficiency in the area [1,12,14]. An improvement in the patient's condition was noted with increased intake of fluids, fruits, vegetables and milk (Tables 5 and 6).

| Table 5 Foods believed aggravate symptoms in SCD patients | |
|---|---|
| Food | Percent |
| Beans (including fava beans) | 55 |
| Chick peas | 28 |
| Black-eye beans | 4 |
| Nuts | 4 |
| Categories are taken from survey responses and are not necessarily exclusive | |

| Table 6 Foods believed symptoms in SCD patients | |
|---|---|
| Food | Percent |
| Fluids (including juices, drinks) | 25 |
| Fruit | 25 |
| Vegetables | 25 |
| Milk | 20 |
| Liver | 12 |
| Meat | 4 |
| Date | 4 |
| Rice | 2 |
| Yogurt | 1 |
| Categories are taken from survey responses and are not necessarily exclusive | |

The study found that 19% of respondents suffered a painful crisis (which might last from a few hours to a few weeks) once a week, 48% once a month, and 33% between one and four times a year. One might expect that school absenteeism would echo the above data: we found that 43% of those responding had experienced irregular schooling due to frequent crisis and 2% had had to discontinue schooling as a result of the severity of SCD. Of those surveyed, 10% had experienced the death of some family member due to SCD. The need of patients for qualified advice was clearly indicated by 70% being in favour of premarital counselling and 62% in favour of specialized sickling clinics (Table 7).

| Table 7 Miscellaneous findings | |
|---|---|
| Finding | Percent |
| Schooling | |
| Regular | 29 |
| Not regular | 43 |
| Stopped | 2 |
| Course of disease | |
| Symptoms became worse | 29 |
| Symptoms became better | 30 |
| Same | 28 |
| Don't know | 13 |
| Frequency of crisis | |
| Weekly | 19 |
| Monthly | 48 |
| Once q year | 14 |
| Premarital counseling is important | 70 |
| Special sickling clinic is important | 62 |
| Death in family due to sickle cell disease | 10 |
| Fully vaccinated | 76 |

## 3. Haematological characteristics of Bahraini sickle-cell disease patients

It is well known that the three major types of haemoglobinopathy are found in Bahrain [1], and many different combinations of haemoglobinopathies genes occur. All may happen with or without the coincidental G6PD deficiency. These complex interactions produce a continuous spectrum of severity, both clinical and haematological [14].

This study was of the haematological picture of Bahraini sickle-cell disease patients. A total of 50 such cases was sampled. The ages of these patients ranged from 15 to 50 years.
We found that 60% of the patients had Hb lower than 10 g/dl and that only 8.8% had Hb above 12 g/dl. The normal Hb for an adult is 12 g/dl or higher [15]. Of these patients, 57% had HCT below 30. MCH was below 25 pg in 64%; the normal level of MCH is 28 pg or above. The low level of MCH in these patients is partly due to the presence of the thalassaemia gene. MCV was also shown to be on the low side_62% had MCV below 76 fl, indicating microcytosis, which is partly due to the coexistence
of the a-thalassaemia gene with SCD [7] (Table 8).

Table 8 Comparison between haematological values of Bahraini SCD patients and those of normal Bahrainis

| Parameter | Mean | SD | SE | Normal |
|---|---|---|---|---|
| Hb | 100 | 1.5 | 0.22 | 141.7 |
| WBC | 10.62 | 5 | 0.67 | 6.67 |
| RBC | 4.09 | 0.75 | 0.11 | 5.03 |
| HCT | 29.7 | 4 | 0.6 | 42.1 |
| MCV | 74.4 | 11 | 1.6 | 82.98 |
| MCH | 24.9 | 0.4 | 0.6 | 27.8 |
| MCHC | 33.4 | 1.4 | 0.6 | 33.3 |
| Retics | 6.87 | 5.4 | 0.7 | |
| RDW | 17.1 | 2.9 | .44 | |
| Hb F | 13.4 | 6.5 | 0.2 | |

See list of abbreviations on page 118 for units

A study was done in Saudi Arabia comparing the haematological values in SCD patients from Eastern Province and those from Western Province [16] (Table 8). These two groups were found to have different haplotypes [17,18]. The Asian haplotypes predominated in the patients from Eastern Province while the African haplotype, benign type or S1 predominated in the patients from Western Province. There were significant differences in the total haemoglobin, red blood cell and haematocrit values, but the red cell indices (mean cell volume), mean cell haemoglobin concentration and the percentage of Hb F did not show any significant difference. If we compare the patient values from our study with these two groups (Table 9), we find that the Bahraini numbers are similar to those from Eastern Province, Saudi Arabia. This is consistent with the results of a molecular study presented later.

| Table 9 Comparison between haematological values for Bahraini SCD patients and patients from Eastern and provinces of Saudi Arabia | | | |
|---|---|---|---|
| Parameter | Bahrain | Eastern Province | Western Province |
| Hb | 100.0 ± 1.5 | 108.0 ± 0.96 | 84.0 ± 1.5 |
| RBC | 4.1 ± 0.75 | 3.9 ± 0.59 | 3.0 ± 0.8 |
| HCT | 29.7 ± 4.0 | 30.0 ± 0.59 | 23.0 ± 0.05 |
| MCV | 74.4 ± 11.0 | 78.5 ± 10.0 | 81.3 ± 12.8 |
| MCH | 24.9 ± 0.4 | 28.6 ± 5.1 | 29.0 ± 5.6 |
| MCHC | 334 ± 1.4 | 36.1 ± 3.6 | 36.1 ± 5.22 |
| Retics | 6.9 ± 5.4 | 6.5 ± 4.2 | 21.6 ± 10.3 |
| Hb F | 13.4 ± 6.5 | 11.3 ± 6.2 | 10.3 ± 7.0 |
| See list of abbreviations on page 118 for units | | | |

## 4. Beta globin gene haplotypes in Bahraini sickle-cell disease patients

Molecular genetic studies were undertaken to determine the haplotypes of chromosomes carrying the sickle-cell allele in Bahraini patients. A total of 59 individuals from 19 families were studied. Of these, 35 were carriers. Haplotypes were investigated by PCR amplification of globin target sequences followed by restriction digestion using Hind III, Ava II, Hind II, and Hinf l polymorphism [19,20]

In the 19 families the Bs gene was found to be linked to the Asian haplotype in 33 chromosomes (90%), to the S2 haplotype in two chromosomes (5%), to the haplotype S1 in one chromosome (2.5%) and to the haplotype found in association with β-thalassaemia in one family (2.5%).

Fig. 1 shows the pedigree of a family with sickle-cell disease exhibiting the Asian haplotype, while Table 10 shows the different haplotypes reported in Africa, Saudi Arabia and Bahrain.

The present study shows that all Bahraini patients with sickle-cell disease studied to date have one haplotype in common_the Asian haplotype. It is present in all the 19 families studied. Of the affected individuals in the 19 families, 27 were homozygous with the Asian haplotypes, five were heterozygous (Asian, S2), two were heterozygous (Asian, S1) and two were heterozygous (Asian, b-thalassaemia).

In Saudi Arabia, four haplotypes were found: the Asian, S2 and S1, together with a rare Saudi haplotype (Kulozik 1986). Kulozik suggests that a West African population carrying the S1 haplotype migrated to North Africa, to the Mediterranean and to the southwest of Saudi Arabia. The Asian Bs mutation may have originated in east Saudi Arabia, spreading to India with the Arab expansion in the first millennium AD, perhaps along the Indian-Arab trade route [9,20,21].

This study indicates that there are at least three different Bs haplotypes in the small islands of Bahrain, and that the Asian haplotype is predominant. The sickle-cell alleles in Bahrain probably derive from different sources, mainly Asian and partly African reflecting the migrating populations that have passed through the country in the past.

① + −

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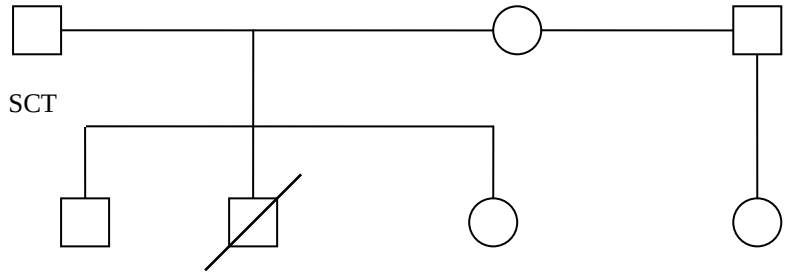


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⑥ - -

| Area | Hind II | Hind III G$\gamma$ | Hind III A$\gamma$ | Hc $\Psi\beta$ | Hind II 5* | Ava II | Hc β | Hind II 3* | Ava II | Hp Hind II | Bam HI Hinf I |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Africa | | | | | | | | | | | |
| S 1 | - | - | - | - | | | + | | + | - | + |
| S2 | - | + | - | - | | | - | | + | + | + |
| S3 | + | + | - | + | | | + | | + | + | - |
| Saudi Arabia | | | | | | | | | | | |
| Asian | + | + | - | | + | | | + | | | |
| S3 | + | - | - | | + | | | + | | | |
| Saudi | - | + | - | | + | | | + | | | |
| S2 | - | + | - | | - | | | - | | | |
| Bahrain | | | | | | | | | | | |
| Asian | | + | | | + | + | | + | + | | - |
| β-thal | | - | | | - | + | | - | - | | + |
| S1 | | - | | | - | + | | + | + | | + |
| S2 | | + | | | - | + | | - | + | | + |

Human β-globon gene cluster showing the position of the polymorphic restriction endonuclase sites. Hc: Hinc II, Hd: Hind III, Ava II, Hp: Hpal, Bam: Bam HI

| List of abbreviations | | | | | |
|---|---|---|---|---|---|
| Short Form | Full form | Unit | Short Form | Full form | Unit |
| Hb | Haemoglobin | g/dl | G6PD | Glucose 6 phosphate dehydrogenase | |
| Hb F | Fetal haemogloin | | | | |
| Hb S | Sickle-cell haemoglobin | | HCT | Haematocrit | l/l |
| Hb H | Haemoglobin H | | MCV | Mean corpuscular volume | fl/cell |
| Hb Barts | Haemoglobin Barts | | MCH | Mean corpuscular haemoglopin | pg/g |
| Bs mutation | Sickle-cell mutation | | | | |
| S1 | Benin haplotype | | MCHC | Mean corpuscular haemogloin concentration | g/l |
| S2 | Bentu haplotype | | | | |
| S3 | Senegal haplotype | | RBC | Red blood cell count | per l |
| SCD | Sickle-cell disease | | Retics | Reticulocytes | % |
| SCT | Sickle-cell trait | | WBC | White blood cell count | per l |

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