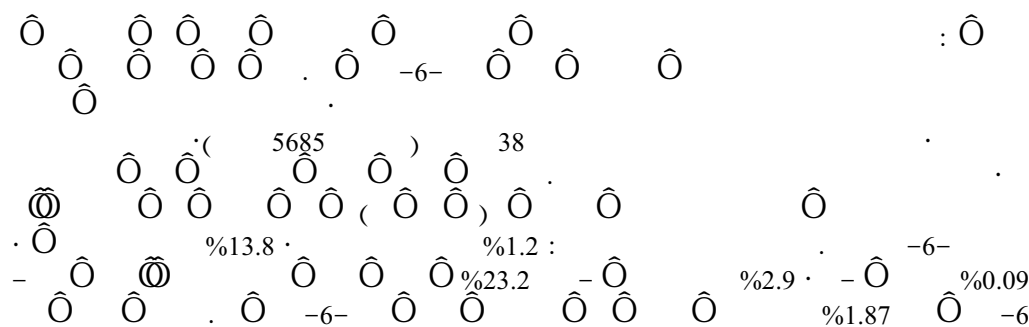


Student screening for inherited blood disorders in Bahrain

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ABSTRACT In Bahrain and neighbouring countries inherited disorders of haemoglobin, i.e. sickle-cell disease, thalassaemias and glucose-6-phosphate dehydrogenase (G6PD) deficiency, are common. As part of the National Student Screening Project to determine the prevalence of genetic blood disorders and raise awareness among young Bahrainis, we screened 11th-grade students from 38 schools (5685 students), organized lectures and distributed information about these disorders. Haemoglobin electrophoresis, high performance liquid chromatography, blood grouping and G6PD deficiency testing were performed. Prevalences were: 1.2% sickle-cell disease; 13.8% sickle-cell trait; 0.09% β -thalassaemia; 2.9% β -thalassaemia trait; 23.2% G6PD deficiency; 1.9% G6PD deficiency carrier. Health education, carrier screening and premarital counselling remain the best ways to reduce disease incidence with potentially significant financial savings and social and health benefits.

Le dépistage des troubles hématologiques héréditaires chez les étudiants à Bahreïn

RESUME A Bahreïn et dans les pays voisins, les anomalies héréditaires de l'hémoglobine, telles que la drépanocytose, les thalassémies et l'anémie hémolytique enzymoprive (G-6-PD), sont courantes. Dans le cadre du projet national de dépistage chez les étudiants visant à déterminer la prévalence des troubles hématologiques génétiques et accroître la sensibilisation parmi les jeunes Bahreïnites, nous avons examiné des élèves des classes de première dans 38 lycées (5685 élèves), organisé des conférences et diffusé des informations concernant ces troubles. L'électrophorèse de l'hémoglobine, la chromatographie liquide de haute pression, le groupage sanguin et la recherche d'une anémie hémolytique enzymoprive ont été réalisés. Les taux de prévalence étaient les suivants : 1,2 % pour la drépanocytose ; 13,8 % pour le trait drépanocytaire ; 0,09 % pour la β -thalassémie ; 2,9 % pour le trait β -thalassémique ; 23,2 % pour l'anémie hémolytique enzymoprive ; 1,9 % pour le portage de la G-6-PD. L'éducation sanitaire, le dépistage des porteurs et la consultation prénuptiale restent les meilleurs moyens de réduire l'incidence de la maladie, avec des économies financières et des avantages sur le plan social et de la santé potentiellement importants.

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Introduction

Inherited disorders of haemoglobin are among the most frequently occurring single-gene disorders in humans, of which sickle-cell disease (SCD) and the thalassaemias are the most common. Glucose-6-phosphate dehydrogenase (G6PD) deficiency, an inherited haemolytic anaemia with disordered red blood cell metabolism, is also common [1–3].

Many studies have shown the prevalence of these diseases to be relatively high in the countries of the Gulf Cooperation Council, i.e. Saudi Arabia, Bahrain, Kuwait, United Arab Emirates, Oman and Qatar, and in neighbouring countries such as Iraq, the Syrian Arab Republic, Jordan, Palestine and Lebanon [4–10].

Bahrain is an archipelago of 36 islands of 694 km², between Saudi Arabia to the west and Qatar to the east. In 1991, the population was estimated to be 500 000, including Bahrainis and non-Bahraini residents (non-Bahrainis are 39.2% of the population). This has increased by 27.7% and birth and population growth rates over the past 5 years have been stable. In 1998, the crude birth rate was 20.3/1000 population and the infant mortality rate was 8.5/1000 live births.

Plasmodium falciparum malaria was endemic in Bahrain until its eradication in 1970. Malaria-associated genetic defects of red blood cells such as SCD, the thalassaemias and G6PD deficiency might therefore be expected to be common [11]. A newborn screening study in 1984–1985 in Bahrain revealed that 200 neonates (2.1% of all births) had SCD, 11.2% were carriers of the abnormal gene for SCD and 20.0% had G6PD deficiency. In a 1994 premarital counselling study in Bahrain, 2%–4% of the study group were carriers for β -thalassaemia [12–16].

In the absence of a cure for these diseases, prevention remains the best option to minimize their impact. The thalassaemia control programme of Cyprus, for example, reduced the incidence of β -thalassaemia major in that country through measures such as health education, carrier screening, premarital counselling and prenatal diagnosis. The success in Cyprus has encouraged other countries to adopt similar measures. Internationally screening programmes have been proven cost-effective in reducing morbidity and mortality. Where screening programmes have continued over several years, they have been shown to reduce prevalence to rates similar to those achieved in Cyprus [17–19].

A prerequisite for designing any programme of prevention and control of inherited blood disorders is access to up-to-date epidemiological data. In Bahrain, national epidemiological data are in need of an update in order to assist planners and policy-makers in the Ministry of Health as they identify priorities and formulate and evaluate policies and programmes for the control of these diseases.

Another important and ongoing aspect of prevention and control is the need for a population to have a high level of awareness and accurate information about a disease that will lead to behavioural change and minimize risk. This is something that Bahrain has sought to address over the past 15 years. Carriers of an inherited blood disorder are usually asymptomatic for the disease. They are commonly unaware of their carrier status and of the potential problems for the offspring of a union between them and another carrier.

The years of young adulthood, e.g. 16–20 years, present a good opportunity for screening and counselling for genetic blood disorders. A young person who is made aware at this age of the potential risk of

having affected children has time to understand and appreciate the significance of the information before choosing a partner and might therefore be less likely to marry another carrier. In Bahrain, screening students before they leave secondary school has the additional benefit to the student of satisfying the government's requirement that they be screened prior to enrolling in college or applying for a job.

To address these issues and others, the National Project for the Prevention of Hereditary Blood Diseases (NPPHBD) was begun in 1999 as a collaborative project between the Ministry of Health, the Ministry of Education, the Rotary Club of Manama and the Bahrain Hereditary Anemia Society. As a part of NPPHBD, the National Student Screening Project was established.

The objectives of the National Student Screening Project were:

- to raise awareness among young people about the disorders in Bahrain and thus to empower them to make informed choices to reduce the risk of these diseases in their future families;
- to determine the prevalence of certain common genetic blood disorders among Bahraini secondary school students, namely, SCD, the thalassaemias and G6PD deficiency;
- to establish a database registry of all affected students;
- to identify the geographic distribution and variation of the disorders;
- to identify the frequency of the rare abnormal haemoglobin (Hb) variants;
- to determine blood group distribution among those screened and to extrapolate to the total Bahraini population;
- when indicated, to perform molecular studies on selected cases to aid greater understanding of the genotypes of these conditions.

Methods

The original plan of the project was to screen the entire 11th-grade student population in Bahrain, i.e. Bahraini and non-Bahraini students between 16 and 17 years old from both government and private school sectors in the second year of secondary school, or 1 year before graduation—a target population of 7000 students. The project took 10-months. This included initial planning, the provision of education sessions, blood collection, laboratory testing, data processing, distribution of disease status cards, data analysis and reporting.

Tasks were assigned to five sub-committees: education, scientific, clinical, laboratory and information. Each committee was responsible for planning and managing its own fieldwork. Overall coordination, evaluation and scientific reporting of the work were the responsibility of the director.

Training programmes were organized to familiarize all participants with the project and the survey. Specifically tailored lectures were given to health educators, nurses, teachers, technicians and students. The training programmes covered areas such as the rationale for the study, the format of the survey, the work plan and the logistics and methods of sample handling. Training and education of teachers and students were organized mainly by the education committee from November 1997 to January 1998, following which lectures were given to students at the schools by the trained teachers, nurses and doctors.

Senior staff trained laboratory technicians. Four technical teams were created, one of which was responsible for visiting schools at a pre-arranged time for collection of blood samples. From each student 5 mL of blood was collected in an EDTA tube, labelled and sent to the laboratory. A

second team was responsible for preparing the blood samples for analysis and for performing electrophoresis using a high-pressure liquid chromatography (HPLC) machine (Bio-Rad Variant Haemoglobin Testing System, Bio-Rad Laboratories, California, Unites States of America) to identify the different Hb variants. Another team performed blood group tests and a fourth team was responsible for G6PD testing [20,21]. All samples were analysed on the same day.

Permission for screening was sought from the students' parents; 81% consented. Students were fully informed about the diseases through education sessions. The demographic information and test results of each student were entered on a coded form. Each student received a card with test results, intended for use when presenting for any future medical check-up or hospital or clinic admission.

Each school received a report detailing the prevalence of the diseases in their school. As part of the awareness-raising effort, 120 educational lectures were given in the schools and more than 30 000 information booklets were distributed.

Results

From the targeted 11th-grade student population of 7000, approximately 81% of parents responded affirmatively to the request for permission to screen their children. This provided a study population of 5685 students from 38 schools (ages ranged from 16 to 20 years and the male-female ratio was 2:3). Bahrainis comprised 86% of the sample (4870 students) and non-Bahrainis 14% (815 students). The prevalence rates of the disorders are shown in Table 1.

Table 1 Prevalence of genetic blood disorders among 5685 11th grade school students in Bahrain

Genetic blood disorder	Prevalence (%)
Sickle-cell disease	1.20
Sickle-cell trait	13.80
β -thalassaemia	0.09
β -thalassaemia trait	2.90
Glucose-6-phosphate dehydrogenase	23.2
Glucose-6-phosphate dehydrogenase carrier	1.87
Hb D	0.56
Hb E	0.02
Hb C	0.00

Sickle-cell prevalence

A total of 68 students were sickle-cell homozygous, i.e. a prevalence of 1.2%. The prevalence of sickle-cell heterozygous students was 13.8%, i.e. 85% of students did not carry the sickle cell gene.

The prevalence of sickle-cell trait (SCT) was regionally variable, with the highest prevalence in the Western region (23%). Other regions of high prevalence included the Northern (22%), Jidhafs (22%), Sitra (21%) and Central regions (20%). Regions of low prevalence were Hamad (13%), Manama (9%), Isa (9%), Muharraq (7%), Riffa (4%) and Hidd (2.7%).

Among affected cases, the values for sickle Hb (Hb S) as a percentage of total Hb ranged from 50% to 90%. In SCD cases, Hb S comprised > 70% of total Hb. In SCT cases, the Hb S ranged from 19% to 40%, with the majority having a total Hb of > 25% Hb S.

All of the students with normal Hb had normal Hb F values (0.5%–0.8%). All students with SCD had Hb F values > 5% (range: 5%–56%), with most between 13% and 23%. SCD patients with high Hb F generally had a milder clinical picture.

β -thalassaemia prevalence

The prevalence of β -thalassaemia homozygosity was 0.1%. There were five cases detected, two male and three female, and all had surprisingly mild clinical pictures. Blood samples from these cases were sent for DNA analysis.

The prevalence of β -thalassaemia trait was 2.9%. This result was similar to previous reports from a premarital study in Bahrain in which 97% of young people were free of the β -thalassaemia gene defect. Some of the regional differences in prevalence in our study were: 5.4% Hidd; 5.3% Sitra; 3.3% Riffa; and 3.4% Hamad. The Western region, the Northern region, Manama and Muharraq had prevalences of only 2%. The percentage of Hb A₂ in β -thalassaemia trait ranged between 4% and 9%.

G6PD prevalence

There were 1319 students identified as G6PD deficiency homozygous, i.e. a prevalence rate of 23.2%. The female carrier rate was 1.9% (106 students); therefore, 74.9% of students were free of the G6PD gene defect.

Higher G6PD deficiency prevalence rates were found in areas such as Sitra (45%), Western region (36%), Jidhafs (34%), Northern region (31%) and Central region (31%). The prevalence was lower in Isa (17%), Muharraq (11%), Riffa (8%), and Hidd (5%).

The prevalence rate among males (homozygosity) was 11.4% and among females (homozygosity) was 11.9%. The female

carrier rate was 1.9%; however, not all female carriers could be detected by this method. Of course, there were no male carriers. Of the students with G6PD deficiency, 55% were female and 45% were male.

Prevalence of other abnormal haemoglobins

Hb D was found in 32 (0.6%) students—30 students were heterozygous and two were homozygous—of whom 25 were Bahraini (0.5%) and 7 were (0.9%) non-Bahraini. Hb E was detected in one student only and Hb C was not found.

Blood group distribution

The blood group O Rh⁺ was the most common (47%), followed by B⁺ (23%) and A⁺ (20%). The least common group was AB Rh⁻ (only 0.3%). Rh⁺ blood groups were found in 94.5% of students and Rh⁻ in 5.5%. Globally, 15% of samples would be expected to be Rh⁻.

Discussion

The 1.2% prevalence of SCD homozygosity in our study is lower than reported in two previous Bahraini studies—the 1994 premarital counselling study (1.6%) and the 1984 newborn screening study (2.1%) [14–16]—possibly indicating that prevalence is gradually declining. This might be attributed to increased community awareness as educational and awareness campaigning in Bahrain started 15 years ago. For a more accurate comparison a newborn screening study would need to be conducted to compare disease incidence.

Previous studies on the natural history of SCD in Bahrain have found the highest prevalence to be for mild forms of the disease and that only 10% of total SCD

patients might be expected to have the severe form of the disease. Some of this latter group may die at an early age [22–26].

The prevalence of SCT in the present study was 13.8%, approximately the same as in the premarital counselling study [16], but higher than the newborn screening study, which reported 11% carrier prevalence [14].

DNA analysis of sickle-cell mutations has shown the Asian haplotype to be the most common in Bahrain. This is similar to the situation in the Eastern province of Saudi Arabia. The mutation is associated with a high level of Hb F and many of those affected are able to lead normal lives [26–28].

In our study, the prevalence of β -thalassaemia among students was 2.9%, which was almost the same as the 1994 premarital counselling study [16]. The highest rates were in Hidd (5.4%) and Sitra (5.3%). To define the precise molecular spectrum of β -thalassaemia, we analysed the mutations causing β -thalassaemia in the Bahraini population. From the 13 different β -thalassaemia mutations that we isolated, we identified the following:

- four mutations of the Mediterranean type: CD39 (C→T); IVSI-1 (G→A); IVSII-1 (G→A); and IVSI-110 (G→A);
- four mutations common on the Indian subcontinent: IVSI-5 (G→C); CD8/9 (+G); CD15 (G→A); and CD41/42 (–CTTT);
- three mutations previously described in the Kurdish people: CD44 (–C); nt-88 (C→A); and nt-101 (C→T);
- one mutation previously described in a Malay individual: CD35 (–C);
- one mutation frequently encountered in the Middle East: IVSI-3' end (–25 bp) [29].

However, four different mutations accounted for 80% of all β -thalassaemia alleles. These mutations were: intervening sequence IVSI-3' end (–25 bp) deletion; CD39 (C→T); IVSI-5 (G→C); and IVSII-1 (G→A) [30,31].

Sickle-cell β -thalassaemia was found in few cases. The clinical picture was expected to vary according to level of Hb A.

There was a high prevalence of G6PD deficiency (25.1%) equally distributed among males and females. G6PD deficiency is an X-linked recessive disorder. The expected higher rate among males was not seen in our study, possibly because of the high frequency of the disease and because many female carriers could not be detected by the qualitative methods used in our study. A 1998 study of Bahrainis under the auspices of France's National Health and Medical Research Institute at the Robert Debre Hospital, Paris [30], revealed that of 38 randomly selected X chromosomes studied, 14 (37%) were the G6PD Mediterranean variant (nt-563 C→T; 188 Ser→Phe). In our study, 21% of all students with G6PD deficiency had SCT and 1.68% had SCD.

Our study confirms the regional genetic heterogeneity in Bahrain. Although the Western region had the highest prevalence rate for SCD (25%) among all regions, its prevalence rate for β -thalassaemia (2%) was the lowest. Hidd region, however, had the highest prevalence rate for β -thalassaemia (5.4%) and the lowest for SCD (2.7%). In contrast, Sitra region had the second highest rate for SCD (21.0%) as well as the second highest rate for β -thalassaemia (5.3%). Sitra also had the highest rate of G6PD deficiency (45.0%), followed by Western region (36%), with the lowest rate observed in Hidd (4%). Riffa had the second lowest rate of G6PD deficiency (8%), a high prevalence of β -

thalassaemia (3.3%), and a relatively low prevalence for SCD (3.7%). The malaria selection hypothesis could explain the higher rates of these diseases observed in Sitra and Hidd as they are small islands surrounded by water. The higher prevalence of β -thalassaemia in Riffa may be explained by the impact of migration from Hidd and Muharraq areas.

Hb E, most frequently seen in people from south-east Asia, was found in only one student (a Bahraini national) in the present study. Neither Hb C, which is common in West Africa, nor Hb O Arab was detected in our study [31–34].

The consanguinity rate in Bahrain is high (40%). The prevalence of homozygous cases in regions such as Sitra and Jidhafs might be high because they are very small traditional communities with high consanguinity rates. In regions where the communities are more mixed, homozygous cases were rare or nonexistent reflecting the dilution of the trait-bearing population through non-consanguineous marriages [35].

In the present study, we did not report on the incidence of β -thalassaemia as the equipment used was not sufficiently sensitive to detect all such cases at this age, especially cases of one and two gene deletions. The carrier state, which is common, is asymptomatic. This disease can be detected with ease only in infancy.

The variant machine was able to detect Hb H disease, a three-gene deletion β -thalassaemia. Previous reports of β -thalassaemia have indicated a high prevalence in the Bahraini population, but this disease causes few clinical problems. Cases of Hb H disease with mild clinical picture are few.

There have been no reported cases of hydrops fetalis (four gene deletion) in Bahrain at the present time.

Five different β -thalassaemia mutations have been identified. The most frequent allele is the Saudi-type poly A signal mutation (AATAAA–AATAAG) followed by the rightward deletion (–alpha 3.7) and the pentanucleotide deletion in IVSI of the α -2 globin gene (GGTAGG–GG), and two less frequent alleles—a leftward deletion (–alpha 4.2); and Turkish type poly A signal mutation, (AATAAA–AATGAA) [36].

Conclusion

The National Student Screening Project was successful in updating national data on the prevalence of inherited blood disorders among students in Bahrain. All participants benefited from this project. Students received their inherited blood disorders status cards. The Ministry of Health received accurate, updated statistics that will help in the planning of future services. The Ministry of Education obtained data on the prevalence of these disorders among students on a school-by-school basis. This information will aid planning to improve the health of Bahraini students.

The project also raised community awareness of the need to reduce the prevalence of these disorders among future generations. Preventive measures such as health education, carrier screening and premarital counselling remain the best ways of dealing with inherited blood disorders. Such measures can provide potentially significant financial savings and health and other social benefits.

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