Review of the spectrum of genetic diseases in Bahrain

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SUMMARY This paper looks at some of the studies on genetic disorders conducted in Bahrain. The disorders covered include: genetic blood disorders, metabolic disorders, chromosomal disorders, including Down syndrome, and cystic fibrosis. The rate of consanguinity in Bahrain and the results of premarital counselling are also discussed.

Introduction

Noncommunicable diseases, especially genetic diseases, are assumed to be a major cause of morbidity and mortality. Genetic disorders are a significant burden on health care delivery systems. Their chronic nature requires life-long medical attention, expensive supportive and symptomatic therapy and specialized care. Effective control of these diseases requires that their natural history, frequency and distribution be studied.

A national committee for the control of hereditary diseases was established in Bahrain in 1993 to conduct population studies with the aim of determining the prevalence of genetic diseases within the country and improving management and treatment standards of patients suffering from these diseases. During the past 14 years, the Genetics Unit of the Bahraini Ministry of Health's Salmaniya Medical Complex (SMC) has carried out many studies in order to provide a picture of the frequency of these diseases within Bahrain. This review considers some of the studies.

Consanguinity in Bahrain

We studied the rate of consanguineous marriage — an historically long-standing practice among Bahrain's different social classes — to see if the frequency of cousin marriages has changed over time, and to ascertain the prevalence of genetic disease [*1*]. A group of 500 young, married Bahraini women each completed a standard questionnaire, which included questions about the family relationship of the husband and wife, and the relationship of their parents. The questionnaire thus provided information about 1000 couples back to the grandparents' generation. The rate of cousin marriage was 39.4% in the present generation and 45.5% in the previous generation, indicating a high rate of consanguinity, decreasing significantly over time. The rate of first-cousin marriage was 21%. Interestingly, while 53% of respondents were in favour of consanguineous marriage, 62% agreed it could cause genetic disease and 47.8% agreed it could cause social problems [*1*]. Table 1 shows the prevalence of consanguineous marriage in Bahrain in the present and previous generations.

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Table 1 **Percentage prevalence of consanguineous marriage in the current and immediately previous generations, Bahrain**

Relationship	Current generation (n = 500)	Previous generation (n = 1000)
Not related	60.6	45.5
Related	39.4	45.5
First cousins	21.0	24.5
Second cousins	7.8	7.9
First cousins once removed	3.0	3.6
Distant relative	6.8	7.1

Congenital abnormalities

A study was carried out to determine the incidence of congenital anomalies in Bahrain by looking at Ministry of Health statistics for the 11-year period, 1980–1990. The incidence of congenital anomalies was found to be 2.7% of live births. Each anomaly was studied separately and, wherever possible, compared with the incidence in other countries. Anomalies of the musculoskeletal system had the highest incidence (2.28 per 1000 births), followed by the genitourinary system (2.13 per 1000 births). The incidence of chromosomal disorders was 0.90 per 1000 births [*2*]. Table 2 shows the annual incidence of each anomaly.

Genetic blood disorders

Several studies have been conducted on genetic blood disorders in Bahrain [*3–7*]. In 1990, hereditary anaemias were the third most common reason for attendance at SMC. In 1986, screening of neonates for haemoglobinopathies using 10 327 cord blood samples found sickle-cell disease

Table 2 **Annual incidence of congenital anomalies per 1000 births, 1980–1990**

Anomaly	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	Average incidence
Neural tube defects	2.18	1.01	1.24	1.46	1.14	1.21	0.54	0.49	0.42	0.44	0.35	0.95
Coronary heart defects	0.49	2.03	2.22	1.63	2.53	2.50	0.53	0.75	0.90	0.58	0.38	1.32
Respiratory	–	–	0.26	0.34	0.16	0.24	0.07	0.08	0.04	0.03	0.05	0.12
Cleft palate	0.39	0.55	0.53	0.52	0.73	0.81	–	–	0.25	0.07	0.05	0.35
Gastroitestinal	0.59	1.02	0.98	1.03	0.98	2.02	0.50	0.66	0.56	0.24	1.27	0.90
Genitourinaiy	0.89	3.69	3.02	2.41	2.36	3.87	0.93	1.27	1.33	0.90	0.65	1.93
Undescended testicle	0.37	1.29	0.89	0.69	0.73	1.53	0.35	0.46	0.37	0.18	0.27	0.65
Hypospadias	0.39	2.03	1.24	1.03	0.82	1.13	0.16	0.49	0.50	0.45	0.13	0.76
Chromosomal	0.79	1.01	0.89	0.77	1.14	1.13	0.42	0.45	0.79	1.06	0.20	0.79
Musculoskeletal	1.78	3.50	2.49	3.00	3.75	4.03	0.90	0.89	0.90	1.06	0.47	2.07
Talipes equinovirus	0.59	2.03	–	1.20	1.22	1.05	0.39	0.42	0.32	0.39	0.18	0.71

(SCD) in 2% of the neonates, sickle-cell trait in 11%, α-thalassaemia in 24% and glucose-6-phosphate dehydrogenase (G6PD) deficiency in 20%. More recently, we have determined that β-thalassaemia carriers comprise 2% of the population.

A further study looked at the nature of SCD in the population. The study was in two parts. One part was community-based, with 100 students with SCD filling in a questionnaire about the disease. The other part was hospital-based, in which the files of 70 SCD patients admitted to SMC with sickle-cell crisis were reviewed. The study found exposure to cold to be the principal precipitating factor of painful crisis (45% of cases), followed by fever (35%) and exhaustion (35%), with the most common symptoms being pain and fever. The main signs were anaemia (92%), hepatomegaly (64%), jaundice (64%) and urinary tract infection (30%). Table 3 shows the common presenting signs and symptoms in SCD patients. It is interesting to note that 73% of these patients considered premarital counselling to be essential.

A third study sought to evaluate the clinical presentation and management of 200 Bahraini SCD patients who attended the SMC Accident and Emergency Department for vaso-occlusive crisis during the period January–March 1994. The male:female ratio was approximately 2:1, with 60% of the group in the age range 15–30 years. Extremity pain was the most common presenting feature (86% of patients), followed by pain in the abdomen/generalized body ache (71%). Most patients (83%) responded to treatment with hydration, narcotic analgesics or non-steroidal anti-inflammatory drugs, and were discharged — suggesting perhaps that Bahrainis may have the mild form of SCD.

Table 3 **Most common presenting signs and symptoms in 200 sickle-cell-disease patients resulting in hospital admission. Bahrain, January–March, 1994**

Sign	Percentage
Anaemia	92.9
Pallor	90.0
Fever	85.7
Body ache	78.6
Headache	77.0
Abdominal pain	71.4
Jaundice	64.3
Hepatomegaly	64.3
Joint pain	62.9
Limb pain	60.0
Chest pain	58.6
Backache	58.6
Splenomegaly	55.7
General infection (not specified)	45.7
Urinary infection	30.0
Dactylitis	22.9
Diarrhoea/vomiting	20.0
Ear, nose and throat problems	17.0
Cardiac complications	15.7
Cholecystitis	14.3
Gall-stones	12.9
Ophthalmological problems	5.7
Priapism	0.0

Molecular aspects of genetic blood disorders among Bahrainis

Molecular genetic studies were undertaken to determine the haplotypes of chromosomes carrying the sickle-cell allele in Bahraini patients, and hence to consider the possible origin of these alleles. A total of 59 individuals from 19 families were

studied, of whom 12 were affected with sickle-cell anaemia and 35 were carriers. Haplotypes were investigated by polymerase chain reaction amplification of the globin target, followed by restriction digestion using *Hin*dIII, *Ava* II, *Hin*d I and *Hin*fI polymorphism.

Within the 19 families, the beta S gene was found to be linked to the Asian haplotype in 33 chromosomes (90%), and to the S2 haplotype in two chromosomes (5%). The Bantu haplotype was found in few patients (only 2.5%), and a haplotype found in association with β-thalassaemia was found in one family (2.5%). The study shows that the Asian haplotype is predominant in Bahrain. This haplotype has been found to be linked to a benign form of sickle-cell anaemia.

In studying the molecular aspects of β-thalassaemia we found a high frequency of IVSI-3 (–25 bp) mutation (40%). This mutation, together with [(CD39 (C→T)] and IVSI-5 (G→C) account for more than 80% of β-thalassaemia alleles in this country.

We found two deletional α-thalassaemia alleles (alpha 3.7 and alpha 4.2), and one non-deletional allele in the alpha 2 gene. The interaction between the deletion alleles and the non-deletion alleles provides a complex picture in phenotype. As for G6PD, out of 35 chromosome, 11 were found to carry the G6PD Mediterranean mutation (nt563 C→T; 188 Ser→Phe) (3.7).

Metabolic screening of neonates

A neonatal metabolic screening study was performed on 1000 neonates, where electrospray tandem mass spectrometry was applied. Blood samples were collected on Guthrie cards from the heels of infants on the 3rd to 5th days of life. The dried samples were mailed to the mass spectrometry laboratory at King Faisal Specialist Hospital where they were analysed for more than 20 metabolic diseases, such as amino acids, organic acids and carnitine esters. The results showed a high incidence of metabolic disease. Annually, we would expect approximately 100 neonates to be affected by diseases such as maple syrup urine disease, medium-chain acyl-Co-A dehydrogenase deficiency, primary systemic carnitine deficiency, methylmalonic acidaemia and methylene tetrahydrofolate reductase deficiency [*8*].

Chromosomal disorders and Down syndrome

The incidence of chromosomal abnormalities was found to be relatively low. The incidence of Down syndrome among Bahrainis is 0.9 per 1000, compared with 1.4 per 1000 internationally.

We studied data collected retrospectively from hospital records for the period 1989–1993 of 104 Bahraini patients with Down syndrome, including those of all Down syndrome patients admitted to the main hospital in Bahrain during the past 5 years. Cytogenetic analysis had been performed on 89 patients. The mean age of patients admitted was 5 years, with 60% of patients under 1 year of age; the oldest patient was 31 years old. The most common complications were chest infections, congenital heart disease, increased susceptibility to all types of infection, anaemias, ear, nose and throat and eye complications.

Karyotyping analysis showed that 97% of those studied had free trisomy, 2% had translocation and one patient had a mosaic

Table 4 **Patients with rare, abnormal karyotype, Bahrain**

Age (years)	Sex	Karyotype	Phenotype
3	F	46,XX,+21 47,XX,–21;22+r(22)	Down syndrome features
Neonate	M	47,X,–4(4;13) (q35q22)mat	Micrognathia, undescended testis, polydactyly (all limbs), hepatosplenomegaly
8	F	46, XXsex,del (17p)	Mental retardation, obesity, brachydactyly, congenital heart disease
6	F	46,XXdel(9) (p22>pter)	Mental retardation, speech defect, synophrys anteverted nares
7	M	46,XY,del(21) (q12;12>pter)	Microcephaly, growth and mental retardation, undescended testis
7	M	46,XY,del(8) (q23q24.1)	Marasmus, inguinal hernia, mental retardation, café-au-lait spot
3	F	46,XX,(6;10) (q15q21–20)	Microcephaly, developmental retardation

F = female M = male

— a very rare karyotype reported for the first time [47,XX,+21/47,–21,–22+r(22)] [*9,10*].

We also performed cytogenetic studies on 500 Bahraini patients suspected of having chromosomal abnormalities on the basis of physical and/or developmental clinical features. We found that 27% of these patients had abnormal karyotypes. Numerical abnormalities were found in 19% of patients (this included trisomy 21) and structural abnormalities in 7%. Table 4 shows patients with rare abnormal karyotypes.

Cystic fibrosis

Cystic fibrosis is an hereditary multisystem disease transmitted as an autosomal recessive disorder. It leads to chronic pulmonary disease, pancreatic enzyme deficiency and abnormally high concentrations of electrolytes in sweat. Our study was an intensive retrospective search for patients with cystic fibrosis from clinical data and hospital records from SMC, with the aim of determining the prevalence of cystic fibrosis in Bahrain [*11*]. The survey included 27 patients confirmed as having cystic fibrosis, born during the period 1978–1994. Almost 200 000 children were born in Bahrain during this period.

Diagnosis was established by the presence of high sodium and chloride (≥ 70 mmol/L) concentrations in sweat. The mean incidence during this period was found to be 1 in 7700. All cases were diagnosed during the first year of life, and 60% were diagnosed in the first 3 months of life. The male:female ratio was 14:13. The incidence of meconium ileus was 16%. Mortal-

Table 5 **Incidence of cystic fibrosis, Bahrain, 1978–1994**

Year	No. of births	No. of cases	Incidence
1978	9 398	2	1:4 700
1979	9 985	0	0
1980	10 097	0	0
1981	11 248	1	1:11 000
1982	11 248	2	1:5 600
1983	11 633	3	1:3 900
1984	12 254	2	1:6 100
1985	12 394	1	1:12 000
1986	12 893	2	1:6 400
1987	12 699	3	1:4 000
1988	12 555	0	0
1989	13 611	1	1:13 600
1990	13 370	1	1:13 000
1991	13 229	3	1:4 000
1992	13 874	2	1:7 000
1993	14 234	3	1:4 700
1994	13 941	1	1:13 000
Total	208 663	27	1:7 700

Table 6 **Premarital screening statistics, Bahrain, 1993–1994**

Group	No.	%
Clients with sickle-cell disease	8/50	1.6
Clients with sickle-cell trait	65/500	13.0
β-thalassaemia carriers	10/500	2.0
Clients with G6PD deficiency	130/500	26.0
Couples at risk of having affected children	13/161	8.1
Consanguineous couples at risk	2/13	15.4
Nonconsanguineous couples at risk	11/13	84.6

G6PD = glucose-6-phosphate dehydrogenase

ity in the neonatal period was 60%. The first-cousin marriage rate among these families was 63%. Table 5 shows the incidence of cystic fibrosis in Bahrain between the years 1978 and 1994.

Premarital counselling

The Genetics Unit and the Maternal and Child Health Department worked jointly to establish a premarital counselling service in 1992. Analysing the data of the first 500 clients attending premarital counselling sessions, we found that 8% of couples were at risk of having children with genetic blood disorders — either SCD or thalassaemia. Only 15% of the at-risk couples were related [*12*]. Premarital screening statistics for the period 1993–1994 are shown in Table 6.

Syndromes seen in the genetics clinic

In our study of patients attending the genetics clinic, we found an increased rate of families with metabolic disorders, spinomuscular atrophies, Noonan syndrome and Lawrence–Moon–Bardet–Beidl syndrome. The study indicated that autosomal recessive type genetic diseases are the most prevalent in Bahrain, while other diseases are rare [*13*].

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