Study of hemoglobinopathies in Oman through a national register

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ABSTRACT

Objectives: A national register of symptomatic hemoglobinopathies has been developed in Oman to facilitate the development of the National Program for the control of genetic blood disorders.

Methods: The information was initially collected retrospectively through hospital records and was refined prospectively with data collected through a survey of pediatricians. The percentages of heterozygotes in different population groups and geographical locations, birth prevalence, age distribution of cases and factors determining frequencies of Hemoglobinopathies in different regions of the country were studied from the register.

Results: The register has identified 1757 cases of homozygous Sickle Cell Anemia and 243 cases of β-thalassemia major in a population of 1.5 million in 1995. Register based national figures of heterozygote carriers approximate 10% for Sickle Cell Anemia and 4% for β-thalassemia major.

Conclusion: Defining regional and tribal variations can assist efficient targeting of health resources. This approach provides a simple model for other countries or regions to follow providing there is a health care system that facilitates registration.

Keywords: Hemoglobinopathies, sickle cell anaemia, β-thalassemia major, genetic register, genetic epidemiology.

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The hemoglobinopathies is an important subject in Oman and other Middle Eastern countries because their high incidence drains health resources and drastically affects family and personal life. Previous studies[1,2] estimated average gene frequencies and served to signal that a significant problem exists. However, the complex tribal structure of the population makes it difficult to interpret surveys of carrier prevalence. Further, more detailed studies were needed to estimate the true birth prevalence and the distribution of hemoglobinopathies within the population. The present study concentrated on symptomatic forms and includes serious disorders due to mutations of the β-globin genes. It actually excludes homozygous alfa-thalassemias which usually do not require medical attention and, for this reason, do not have importance for public health. The collection of national data may assist in planning these services efficiently, so that resources are targeted to the sections of the population that need them most, and used to the best advantage.

Methods. The collection of national data was based on a detailed knowledge of the local health care system. In Oman there is a uniform system of referral from Primary Health Care centers to the Regional Hospitals and the Tertiary Care teaching Hospitals in the capital city (Muscat). Initially it was

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decided to collect data on symptomatic cases. The assumption was made that most patients with symptomatic sickle cell disease or homozygous β-thalassemia would have attended one of the regional or tertiary hospitals in the past 5 years, and thus a hospital-based register should contain an almost complete national ascertainment. All 17 regional hospitals and 2 tertiary care centers participated in the study. It was found that registers of hospital admissions were the best sources of information and they included names, age, sex, place of residence and diagnosis. In tertiary centers information was available through computerized records. Initially data included 3105 cases of sickle cell disease and 781 cases of β-thalassemia. The data was consolidated in a computerized register including details of 4 names (first, father's, grandfather's and tribal), sex, age or date of birth, address, telephone number, hospital numbers, number of hospital admissions, and associated conditions. In order to avoid duplicates the data was sorted in alphabetical order by first names. There were a great number of duplicate entries as more than 30% of cases (932 of sickle cell anemia (SCA) and 273 of β-thalassemia major (BTM)) had been seen in more than one hospital. Numerous discrepancies in the English spelling of Arab names posed difficulties in finding and deleting the duplicate cases, and the standardization of the English spelling of the names was required. Some individuals with similar names (first, father's or grandfather's) had to be differentiated by tribe, age and the place of residence). The hospital folders of cases identified were examined and crosschecked with laboratory results of hemoglobin electrophoresis. Inconsistent electrophoretic results in 129 cases were discussed with the consultant hematologist to ensure correct interpretation. These were due to tests performed on post-transfusion samples and Sickle Cell/ Thalassemia combinations. Hemoglobin electrophoresis results were unavailable for 15% of registered cases, and a careful clinical assessment was made to verify the diagnosis. The majority of these were excluded from the study. Ultimately 1475 cases of SCA (47%) and 548 (70%) of BTM of the initial cohort were removed because of duplications or incorrect diagnosis. The data is kept securely with strict confidentiality. When requested for a clearly defined purpose, anonymized data on regional frequency or age distribution is provided to health officials or researchers. The regional admissions index is kept by senior pediatricians and includes information on new cases, change of address, number of admissions, blood transfusions and availability of infusion pumps for β-thalassemics. The national register is updated yearly from the regional data. At this stage it was not possible to know how complete the ascertainment of cases was. Therefore pediatric units were given a list of registered cases residing in their district, and asked to identify any discrepancies and continuously record all new cases prospectively. To calculate the national birth prevalence, the number of cases born in 1989-1992 was compared with the total number of live births in these years. At the time of the study this group was selected because of 2 reasons. The first was that children born before 1989 could have had a high mortality as tertiary care was unavailable prior to this date, leading to an underestimate of prevalence. The 2nd reason was that children with milder variants of sickle cell disease might not have presented clinically before 2 years of age, also leading to an underestimate of prevalence. The expected number of new cases per year and the prevalence of heterozygotes for Sickle cell and β-Thalassemia were calculated from the birth prevalence of homozygotes. The Hardy-Weinberg method was used for calculations of heterozygote rates and these figures were corrected for consanguinity.[3] Similarly it was possible to calculate heterozygote frequencies in different geographical areas and the individual tribal groups.[4] From the regional birth prevalence figures the expected number of new cases per year was derived. Major factors determining frequencies of Sickle Cell Disorders and β-Thalassemia in the Sultanate of Oman were also studied.[5] The molecular studies of β-globin haplotypes in single random samples from 23 tribes were carried out at St. George's Hospital Medical School in London. Haplotype analysis was performed by restriction fragment length polymorphism (RLFP) polymerase chain reaction (PCR) analysis after confirmation of SCA homozygosity by Amplification Refractory Mutation System (ARMS). Eight restriction sites were tested using Hind II, Hind III, Ava II and Hind I restriction enzymes.[6]

Results. A total 1757 cases of Sickle Cell Disorders were identified by December 1995 (Figure 1), which consisted of 1620 cases identified retrospectively from the hospital records and 137 from one year prospective registration. Since 69 of 137 of prospectively registered cases were newly diagnosed infants, it appeared that retrospective ascertainment had identified 90-95% of symptomatic Sickle Cell Disorders cases in Oman. The retrospective hospital-based study also identified 233 patients with homozygous β-thalassemia with a further 10 cases identified prospectively. This gave a total of 243 cases in Oman by December 1995 (Figure 1). The birth prevalence of symptomatic β-globin disorders in Oman was found to be 1 in 323 liveborns or 3.1 per 1000 livebirths in 1989-1992. This included 2.7 per 1000 livebirths of homozygous SCA and 0.4 per 1000 of β-Thalassemia cases.[3] On average, 118 new SCA cases and 15 of β-Thalassemia cases are expected to be born each year.[7]

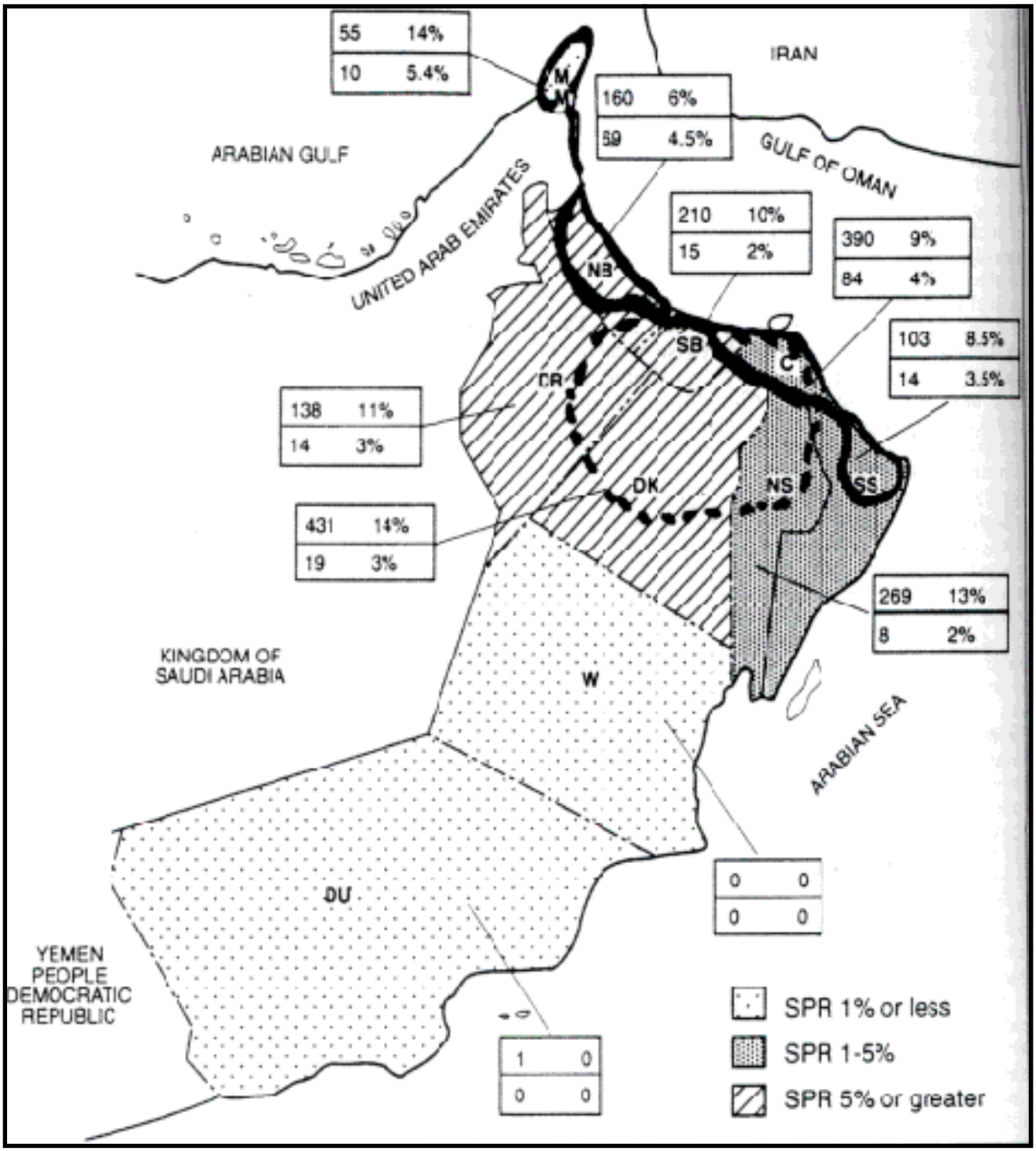

Figure 1 - Regional distribution of symptomatic β-chain disorders in Oman. Sickle cell anemia with calculated heterozygote frequency (upper box) and β-thalassemia with calculated heterozygote frequency (lower box). These frequencies are compared to the smear-positive rate of malaria (SPR) for different regions of Oman. Dotted circular area indicates where over 70% of symptomatic sickle cell disease is found. Area enclosed by thick lines indicate where over 70% of β-thalassemia cases are found.

C- Capital; NB - North Batna; SB - South Batna, DR - Dhahira; DK - Dakhliya; NS - North Sharqiya; SS - South Sharqiya; DU - Dhofar; W - Wusta; MM - Musandam.

Table 1 - Age and calculated survival of those affected with Sickle Cell Disorders.

Age Groups	% of total population	Number of nationals	Number of known cases	Cases/1000	Survival %
0-4	17	246,500	382	2.70	100
5-9	18	261,000	517	1.98	74
10-14	16	232,000	438	1.89	73
15-19	12	174,000	192	1.10	41
20-24	8	116,000	95	0.82	30
25-29	6	87,000	57	0.66	24
30-34	5	72,500	28	0.39	14
35-39	4.5	65,250	19	0.29	11
40-44	3.5	50,750	4	0.08	3
45-49	3	43,500	8	0.18	6
50+	10	145,000	16	0.11	4
TOTAL	**100**	**1,450,000**	**1756**		

There was wide variation in the heterozygote frequencies (Figure 1). As the tribal name was registered in the database, it was possible to study prevalence by tribe.[4] Sickle Cell Anaemia was found to be prevalent in 40% of Omani tribes. However, the uneven distribution within subtribal groups had led to a conclusion that only a third of the tribal population groups have affected members. In almost half of these there were only one or 2 affected sibships. The molecular studies in 23 tribes of Oman identified 46 Benin, 8 Bantu, 6 Bantu A4 and 3 Arab-Indian Sickle haplotypes.[6] β-Thalassemia major was found in less than 10% of Omani tribes. Nearly half of all cases belong to a single ethnic group with an estimated frequency of 7%. The same ethnic group was studied in the United Arab Emirates and found to have predominantly IVS I-5$^{G>C}$ mutation.[8] The age distribution showed that virtually all Sickle Cell cases are under 20 years of age (Table 1). The majority of β-Thalassemia cases are less than 16 years of age. Wide differences in the birth prevalence,[7] regional distributions of both Sickle Cell Disease and β-thalassemia found in Oman (Figure 1) were related to a variety of geographical and genetic factors.[3,4,7]

Discussion. The frequency of hemoglobin gene variants in the Arabian peninsula is amongst the highest in the world. In previous studies from Oman[1,2] only a small sample was studied, and the results were extrapolated to the whole population on the presumption that the conditions are uniformly distributed. The knowledge of the local variations in prevalence, tribal population structure[4] and frequency of consanguineous marriage[3] offers more precise application of the Hardy-Weinberg equation to calculate heterozygote frequency within defined population sub-groups and individual geographical locations. Derived from the Register overall national figures of heterozygote carriers approximate 10% for SCA and 4% for BTM[5] which are higher than previously reported (Table 2). The register provided basic data, on which a variety of detailed epidemiological and genetic studies could be based. In addition to geographical distribution and birth prevalence, the factors determining different frequencies could be studied, patient movements and hospital attendance, age distribution and survival, number of affected sibships and their location. The most important practical achievement was the identification of high- and low-prevalence population groups in Oman. The finding raises questions about how the frequency of these diseases may be reduced. Since prenatal diagnosis is not available in this community at present, other

Table 2 - Heterozygote frequencies of Sickle Cell Anemia and β-Thalassemia in studies from Oman.

Study reference	No. of individuals studied	Hb S	β-Thal
White et al, 1986[1]	1050	0.038	0.024
White et al, 1993[2]	1000	0.061	0.015
Rajab et al, 1997[3]	National register	0.100	0.038

Hb S - Sickle Cell Anemia β-Thal - β-Thalassemia
No. - Number

measures such as health education, premarital counselling and carrier screening are being explored. The data collected for the register will be able to monitor the effects of such interventions on the affected birth rate in the future. There may be cases of asymptomatic sickle cell disease in Oman, as in other parts of the Arabian Peninsula.[9] Such cases would have escaped registration in the present study, which therefore gives minimum figures. The register aimed to give a picture of the impact of the SCA in the population. Deoxyribonucleic acid (DNA) studies suggest that Benin and Bantu haplotypes predominate in Oman, and, possibly, have an impact on survival in the past. Table 1 provides some evidence on the severity and the survival of affected children, although such data should ideally be collected from a prospective cohort. Our clinical impression is that survival is steadily improving. A national register may be inexpensive to set up and maintain where there is a comprehensive health care system. In many Middle Eastern populations the epidemiology of hemoglobinopathies and other genetic disorders may be defined by hospital-based registers of symptomatic cases. It is also practical from the public health point of view to concentrate on symptomatic patients, since this identifies the areas with greatest clinical need. Health costs may be saved through the targeting of resources to high-risk groups. When molecular analysis is used, it may only be necessary to screen each tribe for one common shared mutation. A register may also be used to monitor the effectiveness of public health and education programs. In the future prospective data on the survival will become available and from this a better guide to the clinical effectiveness of treatment will also emerge.

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