Toward prevention of Hemoglobinopathies in Oman

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CHAPTER 2

OMAN: THE COUNTRY AND HEMOGLOBINOPATHIES

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2.1 Geography

The Sultanate of Oman with Muscat as the capital city, is a Middle Eastern country, located in the Arab Peninsula. It covers a total land area of approximately 309,500 km^2 consisting of varying topographic features. Valleys and desert account for 82 % of the land, mountain for 15% and the remaining 3% covers the long 1700 km coastline. Oman is flanked by the Arabian Sea, the Gulf of Oman, the Persian Gulf and the Rub Al Khali desert. The top northwestern part of Oman is bordered by United Arab Emirates, by Saudi Arabia to the west and by Yemen to the southwest. In the past, the country's contacts with the rest of the world were by sea. Today Oman's strategic location on the Musandam Peninsula facing the Strait of Hormuz, plays a vital role for the transit of world crude oil transport. The Rub Al Khali desert forms a barrier between Oman and Saudi Arabia due to difficulty in travelling across. Oman's climate is hot and dry in the interior but humid along the coast and Southern Dhofar.

2.2 Economy

Historically, Oman has always been on the trade routes between the Middle East, India and Africa. Oman's most prominent economical role was in trading and seafaring activities in Zanzibar, East of Africa, and India. Nowadays Oman's main trading partners are United Arab Emirates, China, Korea, Thailand, Italy, Germany, the United Kingdom and the United States of America. Economically, Oman is a middle-income country that is heavily dependent on crude oil, natural gas production, agriculture and fishery.

2.3 Population

According to the last census (2013), Oman's population has risen to 3.87 million inhabitants including more than 500 thousand foreigners coming from Egypt, India, Pakistan, Bangladesh and the Philippines. The population growth rate is about 2% while birth and mortality rates are about 24/1000 and 3/1000 respectively. The median age is 24.7 years, life expectancy is around 74 years and infant mortality rate is 14.5 per 1000 live births. About 50% of the population lives in the capital city, Muscat, and in the Al Batinah coastal region, northwest of the capital. The main spoken language is Arabic but other languages such as English, Baluchi, Sawahili and Hindi are also spoken based on population tribal origins.

2.4 The origin of the Omani population (historic migrations)

The Omani population is heterogeneous, with mixed ethnicity tracking their ancestral roots to neighboring countries via tribal migrations and trading contacts. The main ethnicities are Arab, Baluchi, Sindi and African. Arabs migrated from what was known as Arabia since the 9th century BC onward and settled in Oman. Baluchis originated from Pakistan and the Iranian coasts. Sindhi tribe descends from Indian sailors while others originated from Africa, due to the historical trade between Oman, Zanzibar and Mombasa favored by the Indian Oceans monsoons. Oman was a Portuguese colony from 1508 to 1741, and when the Portuguese were forced out, Oman became an empire that expanded to Zanzibar. This lasted until 1861, when Zanzibar was separated from Omani control. Also many Omanis migrated to India, Pakistan and Iraq looking for a better life. Not until 1971 when native locals started coming back to Oman,

a modern government was established and the wealth of the oil industry was used to aid the people in the country.

Understanding population heterogeneity is important to study the mutation spectrum of disease such as hemoglobinopathies (HBP), which in turn is essential for molecular diagnosis and prevention. We have extensively studied the correlation between ethnicity and molecular spectrum of HBP in Oman. Our results are outlined in chapters 4-8.

2.5 The Omani tribes and their geographical distribution

The north and south parts of the country became united only about 100 years ago. Today the country is divided into eight different governorates (Muhafathat); Muscat, being the capital center, Al Dakhiliyah, Al Batinah, Al Wusta, Al Sharqiyah, Al Dhahirah, Musandam and Dhofar (Figure 2.1). As mentioned above, Oman has a multi-ethnic society in which Arabs constitute the majority. Non-Arab descendants such as the Baloch, who originally migrated to Oman from Iran and Pakistan over several centuries, currently live in Muscat and in the Al-Batinah region. A significant number of tribes of Sindi ethnicity, South Asian ancestry and African origin live in Muscat, along the coasts of Al-Batinah and in the interior regions (1). Some inhabitants of Persian origin are also present in the Musandam region. The existence of multi-origins among the Omani populations would be of a great intrest when studying the molecular spectrum of a disease such as hemoglobiopathies which was identified in this thesis.

Muscat

Muscat is the capital with an area of approximately 1500 km². The city has been known since the second century AD and is considered as one of the oldest in the Middle East. Today Muscat is a large city with residential, commercial and industrialized districts.

Musandam

Musandam is the northernmost area of the country adjacent to Strait of Hormuz, between the Gulf of Oman and the Persian Gulf. This strategic area of 1800 km² is on a vital transit point for the world oil transportation. Musandam is separated from the rest of the country by mountains and a territory belonging to United Arab Emirates.

Al Batinah

Al Batinah is a highly populated coastal area that runs from the lower northern part of Oman, below Musandam, to just above Muscat.

Al Dakhiliyah

Al Dakhiliyah occupies a distinctive location with a belt of mountains on the western side and desert in the south.

Al Wusta

Al Wusta is a flat rock desert in the center of Oman and is populated by the Bedouins.

Al Dhahirah

Al Dhahirah lies towards the west of the coastal areas. It is separated from Muscat by the western Al Hajar Mountains.

Al Sharqiyah

Al Sharqiyah is the eastern region of Oman. It is considered a natural reserve in the country.

Dhofar

Dhofar, at the bottom south and bordering Yemen is a mountainous area covering 99,300km².

Figure 2.1. Map of Oman.

2.6 Religious and cultural practice (consanguinity)

Conversion to Islam in Oman occurred during the lifetime of the prophet Muhammad in the 7th century and the Arab tribes living in Oman were among the first people to embrace Islam. Nowadays the majority of the populations belong to the Abadhi subgroup, comprising 75% of the Muslims in the country. The second Muslim subgroup (the Sunnies) and the third (the Shia'a) are considered a minority in Oman. Omanis tend to be strict observant of their religious

obligations. The government follows the Abadhi subgroup doctrine and appoints a Mufti who has the authority to maintain the Islamic fatwas for the whole country. Culture is deeply influenced by the Arabian traditions and Islamic religion and differs slightly between different groups based on ethnicity, social and tribal stratification.

Consanguineous marriages are very common among Omani as it is perceived to ensure trust and to strengthen family bonds. According to the Oman National Health Survey, 52% of the marriages in Oman are consanguineous (2). Moreover, another large study conducted by Rajab and Patton (3) among more than 60,000 couples reported that 35.9% of the marriages take place between first or second cousins and another 20.4% between members of the same tribes, giving a rate of consanguineous marriage of over 50%. Another study calculated that marriages between first cousins was 34 % and the total consanguinity rate including second cousin relationships and beyond was 58 % (4).

2.7 Hemoglobinopathies in Oman

Hemoglobinopathies are the most frequent autosomal recessive disease in Oman where malaria was endemic. Malaria eradication activities started in Oman in 1971 and included house and open space spraying operations. These measures were followed by rapid reduction in malarial incidence. Most of sickle cell disease (SCD) cases in Oman are found in agricultural areas consisting of a continuous chain of villages situated along the coast, which provided favorable conditions for malaria transmission. One exception is Dhofar, an area with higher rainfall than other regions, abundance of mosquitoes and tropical vegetations but no SCD. The reason is probably due to the presence of a strain of mosquitoes (Anopheles Coustiani) that does not allows the malaria parasite to complete its life cycle (sporogony) efficiently.

In the past, the majority of the Omani patients with severe SCD or β-thalassemia major were not surviving infancy. With advanced health management, early diagnosis and comprehensive treatment, the survival of patients with hemoglobin disorders has significantly improved. Nevertheless, these patients are in need of intensive therapy with poor life expectations and always in need of special support by public health services which in terms have to face economical stress for treatment coverage that is free of charge in Oman.

A comprehensive national program was developed in 1999 in Oman aiming at forming a national committee and a unit in each region specialized in educating and training all regional teams through seminars and workshops and developing a registry document of all cases. By 2003, counseling services were incorporated in community education through mass media taking all ethical, legal and social issues into consideration. Collaboration with experts and reference laboratories of neighboring countries was undertaken, as well as consulting with international western countries was made in order to establish and design a controlled program (Diagnostics and management of genetic blood disorders in Oman, 2008, ISBN number 978-90-807039-3-3).

In spite of the public health improvements made in Oman, patients with hemoglobin disorders are still born at a high rate. For this, a comprehensive knowledge on hemoglobinopathies in Oman had to be derived to prevent the occurrence of such severe conditions and to give a better life to the affected patients.

As previously mentioned, understanding the molecular and genomic make up is essential to be able to improve the health care system, to offer effective prevention programs and

counseling to the families helping them in making the right choice to avoid getting infants with severe diseases.

For this we have studied in this thesis the molecular spectrum of beta and alpha gene defects essential for diagnosis, early screening and risk assessment of the young Omani generation (chapters 4, 5 and 7).

2.8 Mutation spectrum and variability in prevalence in Oman

The annual birth rate in Oman consists of 82, 000 newborn (5). According to Al Riyami et al. the birth prevalence of β-hemoglobinopathies is 3.1/1000 live births while the national incidence of sickle cell disease (SCD) is 2.7/1000 among 2-5 years old children (6).

Various studies have been conducted thus far to calculate the prevalence of different hemoglobin disorders in Oman generating similar or discrepant figures. The first Omani population study on hemoglobinopathies was done by White et al. in 1986 on a relatively small cohort looking for cases with α-thalassemia. Homozygous α^{+}-thalassemia was found at a frequency of 0.39. In 1993 (7), White et al, studied a larger cohort (n=952) and found a higher frequency of homozygous α^{+}-thalassemia (0.45). The frequencies of β-thalassemia trait and sickle cell carriers (SCT) were also estimated to be 0.015% and 6.1% respectively.

From January 2001 to December 2004, more than 30,000 blood samples were collected by Adly et al. and analyzed using the sickle cell solubility method for HbS detection and high performance liquid chromatography (HPLC) for beta gene variant analysis (8). The total prevalence rate of hemoglobinopathies (HBP) was found to be around 8.1%; SCT 7.5 %, SCD 0.46% and 0.102% for other β gene defects (HbD, HbE, HbS-Oman, beta-thalassemia) (8).

In 2003 a large national survey was undertaken by Oman's Ministry of Health in which a total of 6103 households were interviewed and 6,342 children under 5 years of age were screened. The total HBP prevalence rate was 9.5%; SCT (6%), β-thalassemia trait (2%), BTM (0.07%) and SCD (0.2%), Hb D (0.6%), Hb E (0.3%) and Hb C traits (0.02%) respectively (4). Compound heterozygosis of HbS with other abnormal Hb was detected at a very low prevalence (4). When the prevalence of SCT was compared between the different regions, variability in frequency was noted. Al Sharqiya had the highest prevalence (13.9%) followed by Al Batinah (10.8%), Al Dakhiliya (9%), Muscat (8%) Musandam (4.7%) and Al Dhahira (3.9%). The prevalence of β-thal trait was the highest in the Al Batinah region (5.4%) followed by Muscat (2.8 %), Al Sharqiya (2.3%), Al Dakhiliya (2 %), Al Dhahira (1.7 %) and Musandam (1.6 %). The prevalence of SCT and β-thal trait in Dhofar was very low (0.2 %) and no cases were detected in Al-Wousta region (4).

During a neonatal screening program on cord blood samples in 2009, a total of 7,837 Omani neonates were analyzed for complete blood counts and for hemoglobin profile by HPLC. No case with Hb H disease (-α/αα) was detected, α-thalassemia traits were observed with a frequency of 48.5% while β-globin-defects accounted for 9.5% of the samples (4.8% SCT, 2.6% β-thal trait, 0.9% Hb E trait, 0.8% Hb D trait, 0.08% Hb C trait, 0.3% SCD and 0.08% homozygous β-thal) (9). It was also found that the birth rate of newborns affected with major hemoglobinopathies was 4.3/1,000 live births (3.5/1,000 for SCD and 0.8/1,000 for β-thalassemia) (9).

Recently, it was reported that about 400 patients with β-thalassemia major (BTM) and 3,000 with SCD are treated in different hospitals in Oman (10). Around 10 % of Omanis are HbS carriers (10), 2–3 % carries a defect causing β-thalassemia and 45 % are carriers of α-thalassemia (7).

At the genetic level, one study was carried on to decipher the molecular spectrum among beta thalassemia patients which was conducted in 1998 where fifteen different β-determinants were identified (11). Due to the historical migration of the local and trading links with neighbouring countries, ethnic admixing is expected in the country and thus broader spectrum of hemoglobinopathy mutation was needed and this was looked at in (Chapters 4-7).

In year 2000, a study was conducted on Omanie sickle cell disease with the aim to identify the coexisting haplotypes for genetic epidemiology purposes to demonstrate the uni- or multicentric origin and genetic flow of sickle cell mutation in northern part of Oman (12). However, no genotype-phenotype correlation studies were drawn which is important for risk assessment and treatment selection. This association was studied and extended in (Chapters 9-11).

The high birth rate of affected neonates results in huge suffering for patients and families, increasing the financial burden on health resources and for this reason, great attention should be given to appropriate cost-effective prevention strategies and measures. In addition, state of the art medical care has improved the survival age of HBP's and, in absence of prospective primary prevention, the number of patients requiring care in the country is likely to multiply by three times in the next 20 years with a stable population of at least 1,000 patients with BTM and 7,000 with SCD.

Such an increase correlates directly with an increased health burden as patients are largely hospital dependent. At present, the cost of treating all Omani patients with a HBP disorder is estimated to be about 10 million US$/year. In the absence of primary prospective prevention, this will rise to at least $30 million in the next 20 years. Considering the rising costs of treatment, other authors have recently published much higher figures for beta thalassemia reaching levels of 2 million US$ per life treatment for a single patient (13).

To find a sensible solution to this problem, we have evaluated the attitudes of Omani carrier couples towards prenatal diagnosis and medical abortion in chapter 13, showing that primary prevention of hemoglobinopathies by prenatal diagnosis and selective pregnancy termination could be culturally acceptable also in Oman

2.9 The role of public health and religious authorities

Considerable time is needed to establish a developed program for the control and management of severe disorders such as hemoglobinopathies.

As mentioned above, the first community genetic program in Oman was introduced in 1999 by trained regional teams as the national program for the control of genetic blood disorders. The program consists of providing the best possible patient care, raising community awareness through education programmes, screening couples at risk and offering genetic counselling (14). During the last decade, health care in Oman has shown great achievements in medical services in both the preventive and the curative fields and in 2001, Oman was ranked number 8 by the World Health Organization. Although efforts are made by public health centers to raise awareness regarding the burden caused by hemoglobin disorders, a sector of the population still remain unaware of the disease and more efforts should be made by the responsible authorities to inform couples at risk on the meaning of prevention and treatment of these incurable disease.

Especially β-thalassemia major patients need intensive treatment as they present with continuous life-threatening problems. As briefly mentioned above, the disease poses a significant burden not only on patients and families but also on public health due to high costs of medications and treatments, requiring constant highly qualified multidisciplinary care, life-long and frequent blood transfusions and very expensive chelation therapy which are offered for free to all Omani citizens.

Bone marrow transplant (BMT) as the only "curative" option was introduced in Oman in 1995 with a two-bed unit in one of the specialised hospitals. The infrastructure can perform only a few transplants per year, whereas hundreds of patients, of which approximately 72% suffer from β-thalassemia major, remain on the waiting list (15). Although in Oman, due to large families, the possibility of finding human leukocyte antigen (HLA) matched sibling is high, the BMT capacity is insufficient.

Alternatively, primary prevention not only spares the suffering and the burden of expensive treatment, with little hope to become cured, but is also highly cost-effective as it has been shown in many country with a considerable carrier frequency, where offering this option to couples at risk has become established (11).

In Oman, premarital carrier screening service for sickle cell disease and β-thalassemia carrier state is available in all primary health centers. Nonetheless, the service is not mandatory as it is in neighboring Arab countries such as Saudi Arabia (16) and Bahrain (17) and where the incidence of severe hemoglobinopathies has gradually decreased since the carrier screening test has become compulsory prior to marriage.

A study done in the Al Batinah region to estimate the knowledge and the attitude of the population towards premarital testing showed that majority of the responders believed that premarital testing is necessary in Oman. While about half of them supported the option of making this screening mandatory by law about one third was less in favour of being tested before marriage (18). This shows that the level of awareness in the general population still needs more attention by the health affair directorates who are responsible for the development, control and implementation of health policies (10).

Moreover, religious authorities should be made aware of the severity of the condition and of the burden of the disease for an affected child and the family in order to allow free decisions concerning prenatal diagnosis (PD) and pregnancy termination (if indicated) based upon serious medical grounds. Given that religion still contextualises decision making about termination of pregnancy, it is important for policy makers and public health providers to consult the country's main religious scholars to discuss the issue of offering PD to all at-risk couples in the first trimester of pregnancy. Although Islam is one religion, permitting medical abortion in one Islamic country and forbidding it in another is not logical in spite of the fact that it could be explained by the differences of the sub-religion practiced in each country, which includes Shiaa, Sunni and Abadhi. Coming to a common decision that precludes or diminishes human suffering and public health problems which affect a large share of the population in many Muslim countries is therefore highly needed.

2.10 The involved parties (pediatricians, hematologists, laboratories, general practitioner, ethics, politics, insurances)

Multidisciplinary teams are needed to care for patients with severe hemoglobinopathies. Pediatricians, general practitioners (GP) and midwifes are crucial partners of the families that require their patients and their pregnancies, to be managed along with the aid of hematologists, geneticists, laboratory doctors and technicians. Chronic complications manifest 6 months after birth, aggravate with age and need to be managed by an integrated team of devoted specialists including psychologists.

Dedicated medical teams have shown that comprehensive care focusing on the education of patients and their families, may improve physical growth and decrease acute events in sickle cell disease (SCD) children (19). Screening for hemoglobinopathies is usually community based, starting with the GP or the midwife who sees the couple before marriage or the woman early in pregnancy respectively. In case of individual premarital testing, when one partner is found to carry a relevant hemoglobinopathy, the other partner will be offered testing, and if both are found to be carriers, the couple will be offered genetic counseling. This also involves the efforts of a team that will have to rely upon in the work of molecular geneticists and counselors that will provide all data and advice needed for informed reproductive choice (20).

The Omani Ministry of Health follows the Islamic perspectives of medical ethics and world health organization medical policy. The concept of informed consent has been implemented. The patient is given full autonomy to accept or reject a treatment (e.g.: Hydroxyurea for SCD patients) or to choose or not for primary prevention in full patient confidentiality. Although many international health insurance companies exist in Oman, it is not compulsory to have one as it is the case in many countries in the world. Omani nationals receive free treatment in public hospitals thus locals rarely seek to apply and pay for a private medical insurance. Foreign immigrants residing in the country may face financial issues if not insured and since many immigrates who come to Oman, are from countries endemic for hemoglobinopathies (Egypt, Indian, Pakistan, Indonesia and the Philippines), Oman may face the same problem being faced by other western immigration countries (21) in which it may be difficult to reach carriers at risk in the immigrant populations and unable to provide them with sufficient counseling information and thus prevention.

2.11 The implementation of our research

Social medicine is point of care in Oman, a country in which public health has dramatically improved in the last few decades. However, recessive genetic diseases such as hemoglobinopathies remain a substantial burden in the country. Prevention can be dramatically improved by offering prenatal diagnosis and for this, comprehensive molecular studies are required. As mentioned, Oman is a country with a wide range of ethnic groups (3) and thus an extensive spectrum of mutations is expected. Knowledge of the distribution of these mutations is essential in health care planning and management of diseases with a complex molecular pathology such as the hemoglobin disorder. For this, an accurate database with all patients and carriers in all regions with hematological and molecular analysis is needed to aid in the treatment and prevention programs. Advances in this field will be a breakthrough in applied public health science and will put Oman at the state of the art level in treatment and prevention of hemoglobinopathies among Arab countries and worldwide. The aim of this thesis is to

contribute to this process, to reduce the birth prevalence of sickle cell disease, beta- and alpha-thalassemia in the country, with a relevant gain in public health as well as a substantial reduction in treatment related expenses for severely affected patients that are and might dramatically increase in the near future if primary prospective prevention is not implemented (22).

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