Consanguinity, Endogamy and Inborn Errors of Metabolism in Oman: A Cross-Sectional Study

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Key Words

Oman · Consanguinity · Endogamy · Coefficient of inbreeding · Inborn errors of metabolism

Abstract

The Sultanate of Oman, like many other Arab countries, has relatively high rates of consanguinity. Reports suggest that the incidence of inborn errors of metabolism (IEM) is also high in Oman. This retrospective cross-sectional study was designed to evaluate the number of patients with IEM being followed at the only two tertiary centers in Oman treating such patients, and to calculate the consanguinity rates among these families. The electronic medical records of all patients were reviewed for demographic and clinical characteristics. A total of 285 patients with IEM were being followed at the 2 centers involved; 162 (56.8%) were male and 123 (43.2%) were female. The history of consanguinity was documented or available for 241 patients: 229 patients (95%) were born to consanguineous parents related as second cousins or closer. First-cousin marriages were reported in 191 families (79.3%), while 31 patients (12.9%) were born to second cousins. The parents of 5 patients (2%) were related as double first cousins, and 2 patients (1%) were born to first

cousins once removed. The average coefficient of inbreeding (F) in our study was 0.081. Seventeen patients (6%) had associated comorbid conditions other than IEM. Our study highlights the clinical burden of IEM in Oman and emphasizes the high consanguinity rates among the parents of affected patients.

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Introduction

Consanguineous marriage, defined in clinical genetics as a union between 2 people who are related as second cousins or closer [1, 2], is a commonly practiced tradition in the Arab world. Linguistically, consanguinity also refers to the relationship between 2 individuals sharing at least 1 common ancestor. Hence, reports on consanguinity rates may sometimes include marriages between individuals more distantly related than second cousins [3]. The phenomenon of endogamy, defined as marriage within one's own tribe or group as defined by custom or law [4], is also common in the Arab world. Consanguinity rates seem to be increasing for some Arab countries [5–7], and various social, cultural, religious and political

reasons are hypothesized to contribute to the high consanguinity rates seen in different Arab countries [1, 4, 8].

Oman, like many other Arab countries has relatively high consanguinity rates. According to the National Health Survey in 2000, 52% of marriages in Oman were consanguineous [9]. In another, large, clinic-based, cross-sectional study in Oman, 35.9% of marriages were between first and second cousins, and another 20.4% were between individuals within the same tribe. The average inbreeding coefficient (F) was calculated as 0.0198 [10]. The more recently published results of the National Reproductive Health Survey in 2008 showed similar results [11]. Out of 2,388 randomly interviewed couples from all governorates of Oman, 20.6% were related as first cousins, while 25.5% were second cousins or more closely related and 3.6% were distantly related [11].

Although consanguinity does not increase the allele frequency of common disorders, it increases the probability of mating between 2 individuals heterozygous for the same mutant allele. The increased frequency of some recessive disorders in the Arab world has been largely attributed to the practice of consanguineous marriage [3, 12–14]. The tribal structure of some populations in the Arab world along with the practice of endogamous marriage have partly contributed to an unusual burden of rare recessive disorders in these communities [12].

Among the rare disorders that are seen at increased incidence in the Arab world are inborn errors of metabolism (IEM), disorders that are most commonly inherited in an autosomal recessive manner. A total of 82 patients were diagnosed with an IEM in a single center in Oman over a period of 2 years, and 76% of those patients were born to consanguineous parents [15]. Despite the major clinical burden of IEM in Oman, previously published epidemiological studies were largely restricted to a single-center experience, and major categories of IEM were underrepresented in these studies. Our study was carried out at the only two tertiary centers in Oman where patients with IEM are evaluated and managed. The study aims at assessing the clinical burden of IEM in Oman and the prevalence of consanguineous marriages among patients with IEM in the country.

Materials and Methods

This is a retrospective study that was carried out at the Genetic and Developmental Medicine (GDM) clinic at the Sultan Qaboos University Hospital (SQUH) and the Metabolic Unit at the Royal Hospital (RH). These are the only two tertiary centers in the Sultanate of Oman, where all patients with suspected or diagnosed

IEM are being managed. The medical records were reviewed for all patients with an established diagnosis of IEM who are presently being followed. Patients were included if the diagnosis of IEM was confirmed with biochemical studies, molecular genetic testing or both. Patients with a clinical diagnosis of IEM without confirmatory testing were excluded from the study.

The medical records were reviewed to collect demographic and clinical data without any identifying information. Descriptive statistics were used to report the results of the study. Given the retrospective nature of this study and the anonymity of the clinical data collected, no ethical approval was required from either institution.

Results

A total of 285 patients were diagnosed with IEM at the GDM clinic at SQUH and the Metabolic Unit at RH; 162 (56.8%) of them were male and 123 (43.2%) were female. The patients belonged to 130 different tribes spanning 7 different regions of Oman. A total of 97 patients (34%) lived in the Al Batinah region, while 62 patients (21.8%) lived in the Muscat Governorate. Only 4 patients in this study came from the Musandam Governorate. Figure 1 shows the geographical distribution of the patients according to their region of residence in Oman.

A total of 64 different diagnoses of IEM were established for these patients. Table 1 summarizes the main demographic and clinical characteristics of this cohort. The age at diagnosis for these patients varied considerably. Patients as young as a few days old were diagnosed for IEM with an intoxication type of clinical presentation, like urea cycle disorders, or as old as 30 years old, like the patient diagnosed with leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation. Table 2 shows the distribution of patients among the different IEM encountered in this study.

Out of the electronic medical records reviewed for the 285 patients in this study, the history of consanguinity was not explored, not documented or not available for electronic review in 44 patients (15.4%). Of the remaining 241 patients, 229 (95%) were born to consanguineous parents related as second cousins or closer. First-cousin marriages were reported in 191 families (79.3%), while 31 patients (12.9%) were born to second cousins. The parents of 5 patients (2%) were related as double first cousins, and 2 patients (1%) were born to first cousins once removed. When including parental relations more distant than second cousins in the calculations, the prevalence of consanguinity in this cohort reaches 97.9%. The average coefficient of inbreeding (F) was 0.081. Comorbid conditions, defined in this study as medical conditions or health issues not otherwise explained by the underlying IEM di-

Fig. 1. The distribution of patients diagnosed with IEM in this study across the different regions of Oman. The bold numbers denote the different regions: 1 = Al Dakhiliya, 2 = Al Dhahira, 3 = Al Batinah, 4 = Al Buraimi, 5 = Al Wusta, 6 = Al Sharqiya, 7 = Dhofar, 8 = Musandam, 9 = Muscat. The numbers within the boxes represent the number of patients in each region and the respective percentage of the total number of patients diagnosed in the 2 centers of the study, which are both located in Muscat. P = Population size in each respective region. The regional population size is quoted with reference to Oman Census 2010 (www.omancensus.net).

agnosis, were seen in 17 patients (6%). All of these patients were born to consanguineous parents. Three comorbid conditions seen in 3 patients represented other autosomal recessive disorders, namely cystic fibrosis, glycogen storage disease type VI and oculocutaneous albinism. Five patients had congenital heart disease and 2 had nonsyndromic hydrocephalus.

Causative genetic mutations were identified for 127 patients (51.8%). Out of these patients, 3 had X-linked disorders and 2 had mitochondrial point mutations. 121 out of the 122 patients (99.2%) with recessive disorders had homozygous mutations. Only 1 family had compound heterozygous mutations, and the parents of the

affected patient were non-consanguineous. Out of the 42 different mutations identified in different loci, 9 mutations (21.4%) were shared by two or more unrelated Omani tribes each.

Discussion

This cross-sectional study highlights the clinical burden of IEM in Oman. Although the study represents two centers' experience, SQUH and RH are the only two tertiary centers in Oman where patients with suspected IEM are evaluated and managed. The 285 patients diagnosed

Table 1. Summary of the major demographic, gender, and clinical characteristics of patients with various categories of IEM at SQUH and RH (Oman)

IEM diagnostic category	Patients, n	Gender		Mean age at diagnosis (range)	Regional distribution							Prevalence of consanguinity, n (%) [*]
		m	f		MT	SH	D	B	DH	MU	DO	
Aminoacidopathies	57	36	21	4.3 y (1 d to 18 y)	10	16	9	15	4	3	0	50/50 (100)
Organic acidurias	52	30	22	3.8 y (1 d to 14 y)	11	6	6	19	6	0	4	43/44 (98)
Glycogen storage diseases	29	14	15	2.7 y (1 w to 9 y)	9	2	3	10	0	0	5	25/26 (96)
Fatty acid oxidation disorders	12	8	4	13 m (2 d to 10 y)	4	0	2	3	1	0	2	12/12 (100)
Neurotransmitter defects												
BH4 deficiency	10	6	4	15 m (1 d to 5 y)	1	6	1	2	0	0	0	9/10 (90)
NKH	5	3	2	7.5 m (1 d to 2.8 y)	1	0	1	2	0	0	1	5/5 (100)
PDE	1	1		1 m	0	0	0	1	0	0	0	1/1 (100)
Lysosomal storage disorders												
Mucopolysaccharidoses	23	12	11	3.7 y (8 m to 12 y)	7	5	3	8	0	0	0	23/23 (100)
Oligosaccharidoses	1	1		2 w	0	0	0	1	0	0	0	1/1 (100)
Sphingolipidoses	16	8	12	22 m (2 m to 24 y)	1	0	2	11	2	0	0	20/20 (100)
Mucopolipidoses	6	2	4	7 y (2 y to 16 y)	0	0	6	0	0	0	0	6/6 (100)
Lipid storage diseases	4	4		17 m (2 m to 3 y)	0	1	0	1	2	0	0	4/4 (100)
NCL	1	1		after death	1	0	0	0	0	0	0	1/1 (100)
GSD II	5	1	4	3.8 m (3 w to 6 m)	1	0	0	2	0	0	2	3/5 (60)
Disorders of galactose metabolism	16	10	6	11.6 m (1 w to 8 y)	6	5	0	3	0	1	1	16/16 (100)
Mitochondrial disorders												
Nuclear defects	7	3	5	7.2 y (4 d to 30 y)	1	2	0	2	1	0	1	7/7 (100)
Mitochondrial defects	2	2	2	9.8 y (6 m to 30 y)	0	0	1	0	0	0	1	1/2 (50)
Disorders of ketone synthesis or utilization	14	7	7	1.5 y (2 d to 7 y)	4	0	0	8	0	0	2	14/14 (100)
Peroxisomal disorders	2	2		4 m (1 m to 7 m)	0	1	1	0	0	0	0	2/2 (100)
Congenital defects of glycosylation	4	3	1	2.5 y (2 m to 7 y)	0	0	0	4	0	0	0	4/4 (100)
Transporter defects												
BVVLS	2	1	1	15.5 y (15 y to 16 y)	0	0	0	0	0	0	2	2/2 (100)
Cystinuria	2	1	1	1.5 y (18 d to 3 y)	2	0	0	0	0	0	0	2/2 (100)
Wilson disease	7	3	4	7 y (1 w to 16 y)	1	6	0	0	0	0	0	4/5 (80)

BH4 = Tetrahydrobiopterin; NKH = non-ketotic hyperglycinemia; PDE = pyridoxine-dependent epilepsy; NCL = neuronal ceroid lipofuscinosis; GSD II = glycogen storage disease type II; BVVLS = Brown-Vialetto-Van-Laere syndrome; MT = Muscat; SH = Al Sharqiya; D = Al Dakhilya; B = Al Batinah; DH = Al Dhahira; MU = Musandam; DO = Dhofar. ^{*}The denominator used for the calculation of the prevalence of consanguinity represents the total number of patients for whom the history of consanguinity was documented.

with 64 different types of IEM are already a significant increase compared to previously reported data [15]. They collectively serve to emphasize that these disorders are still underrecognized and constitute a significant clinical burden. This may also be supported by the noted underrepresentation of the Dhofar and Musandam Governorates in the regional distribution of patients with IEM, particularly for disorders of small molecule metabolism. Although this may theoretically reflect a lower prevalence of these disorders in both regions, it is also of concern that these disorders may not be recognized early to initiate the appropriate referrals.

The patients with IEM described in this study come from 130 different Omani tribes. The tribal organization typically promotes consanguineous marriages, a situa-

tion that would likely increase the probability of mating between 2 individuals heterozygous for the same mutant allele. This was likely the cause behind more frequent observations of maple syrup urine disease, Wilson disease, isovaleric acidemia, and 3-hydroxy-3-methylglutaryl CoA lyase deficiency in some tribes or regions. Although the same observation may hold true for other disorders, the number of patients diagnosed in other categories are too small to enable a reliable generalization. It is also worth noting that 9 different pathogenic mutations were observed in two or more different tribes, and 6 of those mutations were shared among tribes that were not from the same region. Given how rare these mutations are, this observation provokes the hypothesis of a founder effect. Given the diagnostic repercussions this observation may

Table 2. Number of patients diagnosed with any IEM category

IEM diagnosis	Patients, n	IEM diagnosis	Patients, n
<i>Aminoacidopathies</i>		Niemann-Pick disease	
Citrullinemia type I	2	Type A	2
Homocystinuria	2	Type B	1
Hyperornithinemia with gyrate atrophy	2	Type C	3
Arginase deficiency	3	Sialidosis	1
Classic phenylketonuria	4	Tay-Sachs disease	1
Glutathione synthase deficiency	1	Wolman disease	1
Argininosuccinic acid lyase deficiency	5	GM1 gangliosidosis	2
Ornithine transcarbamylase deficiency	5	Mucopolysaccharidosis	
Tyrosinemia type I	8	Type I	2
Maple syrup urine disease	25	Type II	2
		Type III	18
<i>Organic acidurias</i>		Type VI	1
Biotinidase deficiency	1	Sandhoff disease	2
3-Methylcrotonyl-CoA carboxylase deficiency	2	Pompe disease	5
Ethylmalonic acidemia	2	Mucopolipidosis type IV	6
Glutaric aciduria			
Type I	7	<i>Disorders of galactose metabolism</i>	
Type II	2	Galactosemia	14
L2 hydroxyglutaric aciduria	3	Galactokinase deficiency	1
Methylmalonic acidemia	8	Galactose UDP 4'-epimerase deficiency	1
Propionic acidemia	11		
Isovaleric acidemia	16	<i>Mitochondrial disorders</i>	
		Pyruvate carboxylase deficiency	1
<i>Glycogen storage diseases</i>		MELAS	2
Type I	8	Respiratory chain defects	2
Type III	12	Mitochondrial deletion/depletion	4
Type VI	5		
Type IX	2	<i>Disorders of ketone synthesis or utilization</i>	
Type XIV	2	Beta-ketothiolase deficiency	1
		Succinyl-CoA:3-ketoacid CoA transferase deficiency	4
<i>Fatty acid oxidation disorders</i>		3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	9
Carnitine palmitoyltransferase 1 deficiency	1		
Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency	1	<i>Peroxisomal disorders</i>	
Medium chain acyl-CoA dehydrogenase deficiency	5	Zellweger spectrum disorders	1
Very long chain acyl-CoA dehydrogenase deficiency	5	Primary hyperoxaluria type I	1
<i>Inherited defects of neurotransmitter metabolism</i>		<i>Congenital defects of glycosylation</i>	
Disorders of tetrahydrobiopterin metabolism	10	Type I	1
Non-ketotic hyperglycinemia	5	Type II	3
Pyridoxine-dependent epilepsy (Antiquitin deficiency)	1		
		<i>Transporter defects</i>	
<i>Lysosomal storage disorders</i>		Cystinuria	2
Neuronal ceroid lipofuscinosis	1	Brown-Vialetto-Van-Laere syndrome	2
Krabbe disease	1	Wilson disease	7
Gaucher disease	7		
		Metachromatic leukodystrophy	4
		Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation	3

have, and the implications this may have on primary prevention strategies in the general population, the hypothesis is worth further exploring.

The consanguinity rate of 95% reported in this study is significantly higher than that of the Omani general

population, which is nearly 50% [10]. A similar observation has previously been made in Jordan, where the consanguinity rate among parents of individuals affected with autosomal recessive disorders was around 85%, while it was 25–50% among parents affected with condi-

tions following other modes of inheritance [16]. These two observations serve to argue that consanguinity potentially has a significant role in increasing the propensity for these otherwise rare recessively inherited disorders.

It is worth noting that 17 patients (6%) in this study had associated comorbid conditions that could not be explained by the underlying diagnosis of IEM. Out of those 17 patients, 3 (17.6%) had another recessively inherited condition, while 7 patients had congenital malformations. The latter is in agreement with previous observations concerning the relation between consanguinity and the risk of congenital malformations [17–19]. These observations probably speak for the possible role of consanguinity in increasing the risk for these congenital malfor-

mations in addition to the risk of co-inheritance of more than one recessive disease-causing allele.

This study highlights the significant clinical burden of IEM in Oman, and it emphasizes the role of consanguinity in increasing the predilection for these recessive disorders in countries with high rates of consanguinity. Larger more carefully designed case-control studies may help evaluate this role further in the future.

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