Congenital and genetic disorders in the Sultanate of Oman. First attempt to assess healthcare needs

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Introduction

During the past 40 years, Oman has witnessed remarkable social and economic growth, which is best reflected in the well-organised and efficient healthcare system. As a consequence, a shift in disease pattern has been observed with a significant decrease in the incidence of communicable diseases and decrease in perinatal and childhood mortality (Alwan and Modell 1997; Christianson et al. 2006, 2013). In addition with better standards of medical care for disabled children, many children with congenital disorders are now surviving longer. Accurate information on the prevalence of congenital and genetic disorders in some local populations was occasionally sparse, incomplete or out of date (Alwan and Modell 1997; Christianson et al. 2006, 2013).

This current survey aimed to gain insight into expected caseload of children with congenital or genetic disorders and to assess the future demand for genetic services, and to address policies for developing genetic services in Oman.

Subjects and methods

The ethical and research committee of Oman Research Council and Ministry of Health approved the community-based study which was conducted from January 2009 to March 2012.

The National Census (2007) showed that the total population was 1,850,000 (excluding expatriates). The Omani population is characterised by a rapid rate of growth, a large family size with an average of seven children per family, and a high level of consanguinity (Rajab et al. 2000, 2013). Healthcare is provided free of charge to nationals through over 210 primary healthcare institutions, 11 regional secondary care hospitals, and 3 tertiary referral centres (Fig. 1).

A cross-sectional design based on an Omani population projection for year 2007 was used for calculating sample size and a clear sampling plan. Based on an estimated rate of 7 % of children having congenital or genetic disorders, around 3,000 families were recruited (Modell 2002).

The methodology of the current study was adapted to local difficulties of data collection. In the absence of national medical records, it was assumed that the best way to collect data was to interview mothers. Randomisation was carried out according to a number of inhabitants in cities and villages. Proportionate allocation was also used for each strata (village, town, region) sampling of one female of childbearing age per 600 Omani nationals. The intention was to cover participants close to their places of residence. The interviews were held in primary healthcare centres and regional hospitals. The data were collected through an interviewer and a record of the names of mother and her husband, age, address, profession, income, parity, consanguinity and a detailed family history including abortions, stillbirth, demise in infants and children, malformations, existing morbidity, chronic illness and handicap in children and close relatives (parents, sibs, cousins,

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Fig. 1 Map of Oman showing primary healthcare centres and local hospitals where the study took place

nephews, aunts and uncles). Emotional, social and financial impacts of illness were also recorded. In small families where the mother was relatively young, the grandmother was approached to give the family history.

Maternal descriptions of illnesses and birth defects were recorded together with the available interpretations on the forms and attached to a family questionnaire. These reported illnesses and birth defects reported by mothers were verified with the available medical records including medical records from specialised centres and genetic clinics.

To ensure the quality of the survey, the study supervisors visited each region for meetings with field workers, and a review of collected data and re-evaluation of missing data. Re-interviews were conducted in 100 (3 %) of studied families

and the results were compared against the results obtained by field interviewers in order to control the quality of the survey.

The collected data on miscarriage rate, maternal age distribution, gravidity and consanguinity was compared with such of available national statistical data (Ministry of Health Annual Health Report 2011).

Results

The study took place throughout all areas of Oman in 210 primary health centres across both urban and rural areas (Fig. 1). In total, 3,478 family interviews were collected by 67 interviewers. Incomplete questionnaires were excluded

from the analysis. At the end of the study, 3,063 completed interviews were analysed in depth. One thousand seven hundred and one (55.5 %) family pedigrees were constructed to give an insight into the potential genetic causes for disability.

A comparison of gravidity, abortion rates, maternal age distribution and consanguinity figures in collected data from the current study correlated with available statistical data (Ministry of Health Annual Health report 2011; www.mone.gov.om).

Mortality reporting

In 7.2 % of the completed questionnaires, there was a history of death in infancy or childhood in the offspring. The given reasons for deaths in infancy and childhood are presented in Table 1. In general, terms around one third of deaths reported by mothers were attributed to genetic and congenital disorders, one third to communicable diseases, prematurity or accidents and finally, in one third, there was no known cause for the childhood death.

The causes of death was analysed further by age group. In the newborn, 37 % of deaths were due to lethal malformations, 41 % deaths were for unknown reasons, and the remaining 24 % of deaths were associated with prematurity or multiplex pregnancies. In infancy, only 10 % were attributed to congenital disorders. In childhood, 52 % of deaths were reported as being due to congenital and genetic conditions with familiar recurrence in a third. In childhood, a further 22 % of reported deaths were due to a variety of accidents (e.g. drowning, suffocation, electric shock, snakebites and fall), and relatively few reported childhood deaths after 1 year were due to infection or cancer.

Morbidity data

In addition to looking at childhood mortality, the questionnaires also addressed questions of chronic childhood illness. In the sample, 316 mothers (10.4 %) reported significant childhood illness or disability with familial recurrence in about 30 % of cases (Table 2). In the group with familial recurrence, autosomal recessive disorders were most frequent with a high frequency of haemoglobinopathies. Intellectual disability was reported by 140 mothers (45 %) who had a child with significant childhood illness or disability and a quarter of these children with intellectual disability had affected sibs. In the majority of cases, the cause of intellectual disability was undefined (Table 2).

Consanguinity was recorded in the questionnaires. In the majority of cases, there was a degree of consanguinity. In 1,616 mothers, there was some degree of consanguinity and in 1,447, there was no consanguinity. In the non-consanguineous

Table 1 Reasons for demise reported by mothers

Reason of demise	No.	2–5 Deceased	ICD
Newborns death of undefined reason	20	6	
Infant death of unknown reason	44	18	
Child death unknown reason	13	3	
Birth asphyxia	4	1	P 21.0
Cerebral palsy	8	1	G 80.0
Intellectually disabled children death	10	1	F 73
Chromosomal rearrangements	2	0	Q 00
Autosomal recessive disorders			
Sickle cell anaemia	3	1	D 57.0
Beta thalassemia	1	1	D 56.1
Congenital myopathy	1	0	G 71.2
Epidermolysis bullosa	1	0	Q 81.8
Cystic fibrosis	2	0	E 84.0
Congenital adrenal hyperplasia	1	0	E 25.0
Other congenital disorders			
Multiple congenital anomalies	14	4	Q 87
Anencephaly	3	0	Q.00.0
Congenital hydrocephalus	3	1	Q 03
Hydrops fetalis	2	0	O 36.2
Intestinal malformations	2	0	Q 43.8
Renal malformations	2	2	Q 54.9
Congenital heart disease	9	2	Q 24.9
Down syndrome with congenital heart disease	2	0	Q 90.9
Spina bifida	1	0	Q 05
Congenital heart block	1	0	I 45.9
Cardiomyopathy	1	0	I 42.9
Severe postnatal growth failure	2	1	M 89.2
Childhood malignancies	2	0	C 00
Prematurity	20	9 Twin pairs	P 07
Post vaccination complications	2	0	G 03.8
Communicable diseases			
Febrile illness in infants and newborn	21	3	A 41
Gastroenteritis	6	0	A 09.0
Meningitis, brain abscess	4	0	A 39.9
Measles	1	0	B 05
Pneumonia	1	0	J 16
Accidental death and Road traffic Accidents	14	0	W 00
	223		

In total, 223 (7.3 % among 3,063 interviewed) reported demise in offsprings

mothers, there was still a significant proportion (8.3 %) with significant childhood illness or chronic disability but the frequency of reported cases of intellectual disability was reduced.

Table 2 Range of congenital disorders reported by mothers

	No. of families	2–4 Affected	ICD		No.	2–4 Affected	ICD 10/omim
Conditions with intellectual disability	116	18		Known single-gene disorders	18	10	
Intellectual disability unspecified	72	11	F 79	Spinal muscular atrophy	2	1	G 12.0
Cerebral palsy with intellectual disability	6	3	G 80.0	Barter's syndrome	1	1	
Intellectual disability with cataract	1	1	F 79	Cong adrenal hyperplasia	1	1	E 25.0
Intellectual disability with seizures	4	1	F 79	Nesidioblastosis	1	1	K 86
Brain malformations	2	0	Q 04.3	Maple syrup urine disease	1	1	E 71.0
Primary microcephaly	3	0	Q 02	Galactosaemia	1	0	E 74.2
Congenital hydrocephalus	6	1	Q 03	Pseudohypoaldosteronism	1	1	E 26.9
Epilepsy	7	0	G 40.3	Vit D resistant ricket	1	0	E 55.9
Down syndrome	15	1	Q 90.9	Joubert syndrome	1	0	Q 89.7
Psychiatric disorders	4	0	F 00	Bardet–Biedl syndrome	3	2	Q 87.8
Learning difficulties	20	9	F 70	Oculocutaneous albinism	1	0	E 70.3
				Oro-facio-digital syndrome I	1	0	Q 87.0
Isolated physical handicap	14			Polycystic kidneys	2	1	Q 63.9
Unspecified physical handicap	4	0	Q 68				
Skeletal dysplasias	3	1	Q 77				
Limb malformations	5	1	Q 73	Genetic blood disorders	47	27	
Post prematurity paralysis	1	0	G 80.9	Sickle cell anaemia	40	23	D 57.0
Post polio palsy	3	0	A 80.3	Beta–thalassaemia	2	1	D 56.1
				Haemophilia VIII	1	1	D 68.2
Congenital disorders and anomalies	42 (13 %)	3		Congenital haemolytic anaemia	4	2	D 55
Congenital heart defects	14	1	Q 24.9				
Congenital heart block	1	1	I 45.9	Haematological cancers	4	0	C 90
Spina bifida	2	0	Q 05	Systemic lupus	2	0	M 32
Facial clefts	5	0	Q 35				
Gut malformations	4	1	Q 43.8	Miscellaneous			
Renal dysplasias	2	0	Q 54.9	Hypomelanosis of Ito	1	0	Q 81.9
Thyroid dysplasia	1	0	E 07	Rett syndrome	1	0	F 84.2
Multiple congenital anomalies	2	0	Q 87	Neurofibromatosis	1	0	L 81.4
Hypospadia	2	0	Q 54	Colonic polyposis	1	0	D 17.5
Polydactyly	3	0		Haemolytic uraemic syndrome	1	0	D 59.3
Hernias	2	0		Familiar childhood diabetes	1	1	E 10
Ambiguous genitalia	2	0		Growth disorders	12	2	M 89.2
					18	3	
Congenital deafness	10	3					
Vision defects	23			Congenital CMV	1	0	B 90
Congenital blindness	5	1	H 54				
Congenital nystagmus	1	1	H 55				
Congenital cataract	1	1	Q 12.0				
Ocular malformation	4	1	H 44.9				
Congenital corneal opacity	2	1	Q 13.3				

Congenital disorders contributing to morbidity reported by 10.3 % (316 out of 3,063) interviewed mothers. In the remaining 89.7 % (2,747 out of 3,063 of mothers) all children were reported to have good health

Morbidity pattern in extended families

In the study, 1,701 extended family pedigrees were collected and in 601 pedigrees, there was a record of significant illness

or disability. In the majority of records (588 out of 601) there was a history of congenital or genetic illness. In some pedigrees, the number of affected individuals was considerable. Over half of the reported morbidity (52.4 %) was associated

with intellectual disability (Fig. 2). Inherited blood disorders, congenital blindness and deafness and other disabilities contributed to morbidity in extended families (Fig. 2).

Familiar recurrence was reported in 42 % of families with inherited blood disorders, 29 % with blindness and deafness, 17.5 % with isolated physical handicap and 12 % for various other congenital defects.

Discussion

There are considerable difficulties in the accurate data collection on congenital and genetic disorders in a complete population and this is especially difficult in a developing country (Al-Gazali et al. 2006; Costello A and Tomkins A, 1997; Christianson et al. 2006, 2013 Penchaszadeh et al. 1999). Many of the population studies have been restricted to subpopulations based on hospital studies rather than community-based or population-based studies (Al 1996; Dawodu et al. 2005; Topley and Dawodu 1995; Rajab et al., 2005; Rajab and Patton, 2012) and may not always provide a balanced picture of the frequency or distribution of childhood disability. In Oman, there is a comprehensive provision of government-funded healthcare throughout the country with a network of primary care centres and secondary care hospitals with three major specialist centres for tertiary care (Rajab et al., 2013). This has allowed us to carry out population-based studies on haemoglobinopathies (Rajab and Patton 1997, 1999; Rajab et al. 2000), and on consanguinity (Rajab and Patton 2000). The national tertiary care facility has also allowed us to attempt complete ascertainment using the neurosurgical records for neural tube defects (Rajab et al. 1998). The national coverage for clinical genetics has made the present study possible.

The current study indicates a significant percentage (7.3 %) of mothers reporting death in their offspring. An unknown cause of death were more common in newborns and infants, compared to those dying later in childhood. It was not possible

to independently ascertain all the causes of death but the cause of death was confirmed in 10 % of deceased infants and in over half of those who died later in childhood. The absence of post mortem examination does limit the diagnosis in some situations where the internal malformations may not be fully appreciated.

The current study showed 10 % of Omani mothers reported offspring with morbidity from significant childhood illness or congenital disorders, and in a third of them, there were multiple affected offspring. Similar data was derived from another recent study on effects of consanguineous marriage and adverse pregnancy outcomes with 10 % of Omani mothers reported their pregnancy resulted in an unhealthy baby (Bittles A, personal communication).

The reported diagnoses were checked with hospital records and were usually based on the diagnosis made by senior paediatricians. The more specialised genetic diagnoses were made in the tertiary care hospitals and National Genetic Centre where some specialised genetic testing and diagnostic facilities were provided (Rajab et al., 2013).

The information gathered from family pedigrees reflected an important way of recording members of extended families. It demonstrates an important characteristic of Arabian families, which is the knowledge of kinship and high probability to reach members of the extended family.

The perception of mothers about health status in extended families in pedigree records was similar, with a third of pedigrees indicating morbidity from congenital causes, over half of morbidity from conditions with intellectual disability and a third of affected pedigrees with multiple affected.

The high prevalence of congenital disorders in the community may be contributed to customary consanguineous marriages (Rajab and Patton 2000; Bittles 2003; Zlotogora 2002), improved survival of disabled children and large family size. First and second cousin marriages constituted 24.1 and 11.8 % of all marriages, respectively (Rajab and Patton 2000), with a further 20.4 % of marriages within specific tribal groupings.

Fig. 2 Pie chart showing distribution of morbidity derived from pedigrees. Congenital disorders with intellectual disability (including Down syndrome) accounted for over half of conditions reported, genetic blood disorders contributed to 11 %, congenital deafness 8.3 %, congenital

defects of the vision 11.5 %, various conditions with congenital anomalies 7 %, isolated physical handicap 6.6 %, neurodegenerative disorders 1 % and miscellaneous conditions 2 %

Studies outside Oman have indicated that consanguinity may play a part in the frequency of childhood disability. A study of intellectual disability and cerebral palsy in a consanguineous Pakistani community residing in Bradford area of UK showed a high prevalence of genetic disorders causing disability (Corry 2002). Another 5-year prospective study in a Muslim Pakistani community in the Birmingham area in UK demonstrated a threefold increase of post neonatal mortality and childhood morbidity in the offspring of consanguineous Pakistani parents (Bundey and Alam 1993).

The high morbidity and mortality reported from non-consanguineous unions might seem surprising but probably can be explained by the fact that couples who regard themselves as unrelated may be actually related, because marriage within the tribal boundaries has been a long-established tradition in Oman over many previous generations. Never the less, the current study did demonstrate some decrease in mortality and morbidity in the non-consanguineous mothers and this was most significant in the frequency of intellectual disability.

The current study indicates that consanguinity levels in Oman have not changed significantly in the recent years, which suggests that further reduction of perinatal and childhood mortality and morbidity in Oman would require more attention to preventive genetic services including the application of genetic testing. The number of surviving affected children also increases with a prospect of a considerable burden on the healthcare and social services. Conditions with intellectual disability cause the greatest burden to families and communities and required further research and prevention. Oman healthcare is facing a challenge of drawing the line between the freedom for marital choice and finding solution for the current situation in agreement with local customs and social norms.

Rising awareness among medical professionals about genetic disorders, improvement of biochemical and genetic diagnostic facilities and prioritisation of research on genetic disorders will be required to reduce current diagnostic gaps. The development of a policy model for the early investigations of children with congenital and genetic disorders is critical for further improvement of care with strategy for diagnosis, counselling, prenatal diagnosis, pregnancy care and neonatal screening. More accurate data regarding birth defects and genetic conditions may be collected through central notification of congenital and genetic disorders and environmental statistics. As suggested by Christianson (Christianson et al. 2013), further medical education in the understanding of genetics, and the development of professional skills and experience for dealing with congenital disorders are important points to consider. There is also a need for the involvement of the community, and

improved communication with the public and their understanding of issues involved in care and prevention.

Although there were some limitations in the current study, our findings justify future healthcare planning and interventions for congenital and genetic disorders, in view of their significant financial, social and research relevance.

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