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Spectrum of Paediatric Lysosomal Storage Disorders in Oman

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طيف اضطرابات الاختزان في الجُسَيْمَاتِ الحَالَّة عند الأطفال في عُمان

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الملخص: **الهدف**: دراسة طيف اضطرابات الاختزان في الجُسَيْمَاتِ الحَالَّة عند الأطفال في عُمان. طيف اضطرابات الاختزان في الجُسَيْمَات الحَالَّة هي مجموعة غير متجانسة من الأمراض الأيضية الموروثة. هناك دراسات قليلة حول انتشار هذه المجموعة عند الولادة وبعدها في شبه الجزيرة العربية. **الطريقة**: قمنا بدراسة 86 طفلا مصابا باضطرابات الاختزان في الجُسَيْمَاتِ الحَالَّة تم تشخيصهم خلال تسع سنوات، من يونيو 1998 إلى مايو 2007. وقد تم جمع البيانات السريرية المفصلة، بما في ذلك السن عند بداية المرض والجنس وطريقة بدء المرض ووجود صلة القرابة. **النتائج**: تشير البيانات المتوفرة إلى أن انتشار طيف اضطرابات الاختزان في الجسيمات الحالة في سلطنة عُمان 1 لكل 4700 ولادة حية. وكانت الشحامات السفينغولية المجموعة الأكثر شيوعا بنسبة (47.7%)، تليها الليبوفوسينية السيرويدية العصبية (23.2%) من ثم عديد السكاريد المخاطي (23.2%). كانت نسبة زواج الأقارب عالية إذ بلغت 87.5%. **الخلاصة**: تمثل المعطيات مدى انتشار اضطرابات طيف اضطرابات الاختزان في الجسيمات الحالة في سلطنة عُمان، والتي تُعد من أحد أكثر مجتمعات الشرق الأوسط في انتشار زيجات الأقارب.

مفتاح الكلمات: اضطرابات تخزين الجُسَيْمَاتِ الحَالَّة، عُمان؛ انتشار؛ العرب.

ABSTRACT: ***Objectives:*** The aim of this study was to look at the spectrum of paediatric lysosomal disorders in Oman. Lysosomal storage disorders (LSDs) are a heterogeneous group of inherited metabolic diseases. Few studies on the birth prevalence and prevalence of LSDs have been reported from the Arabian Peninsula. ***Methods:*** We studied 86 children with LSDs diagnosed over a period of nine years, from June 1998 to May 2007. Detailed clinical data, including age of onset, sex, age and mode of first presentation, and presence of consanguinity were collected. ***Results:*** Our data showed the combined birth prevalence for all LSDs in Oman to be around 1 in 4,700 live births. Sphingolipidoses was the most common group of disorder encountered (47.7%), followed by neuronal ceroid lipofuscinoses (NCL) (23.2%) and mucopolysaccharidoses (MPS) (23.2%). The proportion of consanguineous marriages in our series was found to be 87.5%. ***Conclusion:*** Our data represent the birth prevalence and clinical spectrum of such disorders in Oman, one of the highly consanguineous societies in the Middle East.

Keywords: Lysosomal storage disorders; Oman; Prevalence; Arabs.

Advances in Knowledge

- *This is the first report of lysosomal storage disorders (LSDs) from Oman. The study highlights the birth prevalence, spectrum, and clinical characteristics of various disorders, and their relevance in a population with a very high consanguinity rate.*
- *The study's findings add to the knowledge of hereditary disorder screening in the people of the Arabian Peninsula.*

Application to Patient Care

- *Knowledge of LSDs will direct appropriate and necessary testing programmes for patients in Oman.*
- *The importance of high-risk testing lies in the prevention of LSDs by premarital and prenatal screening, as well as in early initiation of treatment, when available.*

Lysosomal storage disorders (LSDs) are relatively rare inborn errors of metabolism, with a combined global birth prevalence of 1 in 1,500 to 7,000 live births.[1] They represent a group of more than 40 distinct genetic disorders.[2,3] Deficiency of lysosomal proteins or,

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less frequently, non-lysosomal proteins involved in lysosomal biogenesis, result in the accumulation of non-metabolised macromolecules.[4] Most of these disorders are inherited in an autosomal recessive manner, except Fabry's disease and mucopolysaccharidoses type II (MPS II) which are inherited in an X-linked recessive manner.[4]

Major groups of LSD disorders include MPS, lipidoses, glycogenoses, and oligosaccharidoses.[4] Most disorders present clinically with multi-system involvement. Common clinical features involve bony dysplasia, hepatosplenomegaly, central nervous system dysfunction, haematological abnormalities, and coarse hair and facial features. There are many phenotypical similarities within the categories. Potential treatments for some of these disorders are available in the form of enzyme replacement therapy (ERT) and bone marrow transplantation (BMT).

Most of the reports on LSD's birth prevalence and general prevalence are from Western countries.[4–9] Data on the frequency of LSDs in the Arab population are quite sparse; however, a recent report described prevalence of inborn error of metabolism (IEM) in Oman.[10] The aim of this study was to investigate the relative frequency of various LSDs in Oman. Estimating the baseline birth prevalence is of increasing importance given the interest in newborn screening for LSDs, and the availability of expensive ERT and substrate reduction therapy.

Methods

Sultan Qaboos University Hospital (SQUH) in Muscat, Oman, is the main referral centre for metabolic genetic diseases in the country. We studied 86 paediatric cases referred over a period of nine years from June 1998 to May 2007. The institution's ethical committee approved the study. Detailed clinical data, including sex, age of onset of disease, age at diagnosis, mode of presentation, family history, consanguinity rates, and high-risk screening results were collected. Detailed results of laboratory investigations and medical imaging were obtained. The Willink Biochemical Genetics Unit in Manchester, UK, (which has UK Clinical Pathology Accreditation [CPA]) assessed the lysosomal enzyme levels from blood samples of all patients. All patients in this study had a confirmatory enzymatic diagnosis. Genetic mutation analysis was only performed in cases of patients who received enzyme replacement therapy (ERT) or a bone marrow transplant (BMT). We determined the annual number of live births in Oman from the National Health Statistics for the years in which our study subjects were born. The total number of live births and the total number of LSD patients then were averaged to a total number of cases per year. The birth prevalence rate of LSDs was calculated by dividing the average number of postnatal diagnoses per year by the average number of live births per year between 1998 and 2007.

Results

Between June 1998 and May 2007, a total of 86 patients (male to female ratio = 1:0.7) were diagnosed with LSD. The average number of live births during the study period was 45,000 per year. The combined birth prevalence for all LSDs was therefore 1 in 4,700 live births per year. Sphingolipidoses as a group was the most frequent LSD (47.7%), followed by neuronal ceroid lipofucinoses (NCL) (23.2%) and MPS (23.2%). Detailed frequencies of LSDs are presented in Table 1. The proportion of consanguineous marriages in the referred families was 87.5%, and 35% of patients had a sibling with a similar illness at the time of diagnosis. The patients ranged in age from 3 days old (neonates) to 18 years of age. A total of 47.5% patients became symptomatic between 1 and 6 months of age, 27.5% between 6 months and 1 year old, and 25% presented with symptoms after one year old. Among sphingolipidosis, Sandhoff disease was one of the most commonly encountered diseases (15.1%), followed by Gaucher disease (8.1%). Late infantile neuronal ceroid lipofuscinosis (NCL) was the single most common disease diagnosed in our series (23%). The majority of these patients presented between 1 to 4 years of age with regression in their development and intractable seizures. It was noted that all the children with disease had myoclonic seizures, microcephaly and maculopathy. In general, global developmental delay/regression (40%), coarse facial features and hepato-splenomegaly (30%) were the most common presenting features at diagnosis. Other presenting features were nystagmus, abdominal distension, deafness, recurrent infections, and failure to thrive.

Table 1: Number of patients and relative frequency of different categories of lysosomal storage disorders (LSDs)

Diagnosis	SUB-Types	No.	%
Sphingolipidoses		**41**	**47.7**
Gaucher disease			
	Type 1	2	2.3
	Type 2	1	1.2
	Type 3	4	4.7
Niemann-Pick disease A and B		3	3.5
Metachromatic leukodystrophy		8	9.3
Krabbe disease		1	1.2
GM1 Gangliosidosis		4	4.7
Tay-Sachs disease		5	5.9
Sandhoff disease		13	15.1
Mucopolysaccharidoses		**20**	**23.2**
	Type I	3	3.5
	Type II	2	2.3
	Type III	7	8.1
	Type IV	4	4.7
	Type VI	3	3.5
	Type VII	1	1.2
Mucolipidosis		**1**	**1.2**
	I cell disease	1	
Oligosaccharidoses		**2**	**2.3**
	Siladosis	2	
Lipid storage diseases		**20**	**23.2**
	Late infantile neuronal ceroid lipofuscinoses	20	
Lysosomal glycogen storage disease—Pompe's disease		**2**	**2.3**
Total		**86**	

A couple of patients were diagnosed by testing done to siblings previously diagnosed with the same disease.

Discussion

The LSDs are rare disorders resulting from the accumulation of substrates within the lysosomes. These disorders are under-diagnosed and their birth prevalence is underestimated.[1] The exact birth prevalence of LSDs in the Arab population remains unknown. This is the first report of LSDs in Oman which highlights the birth prevalence, spectrum, and clinical characteristics of the various disorders identified during a nine-year period. It is also one of the few studies to report the birth prevalence and prevalence of LSDs in one of the highly consanguineous societies of the Middle East. In our study, we estimated the combined birth prevalence rate of LSDs at 1 per 4,700 live births. In Australia, the birth prevalence rate was estimated to be 1 per 9,000, excluding prenatal diagnosis.[4] Poorthuis *et al.* reported the combined birth prevalence for all LSDs in the Netherlands as 14 per 100,000 live births.[5] In Oman, the birth prevalence rate of all inborn errors of metabolism as a group was reported as 1 per 1,555 out of which 25% were LSDs.[10] This is a much higher birth prevalence than that reported in Caucasians. In Saudi Arabia, 125 cases of LSDs of different types were reported in births occurring over a three-year period.[9]

Sphingolipidoses was the most frequent LSD encountered in our study. These cases constituted 47.7% of cases. This finding was consistent with and comparable to different reports. Many of these disorders present in infantile form. In our group, 45.7% of the patients developed symptoms between the ages of 1 and 6 months. Sandhoff disease was one of the most commonly encountered diseases (15.1%). It is a relatively rare metabolic disease, but seen more commonly in certain populations, including the Argentinean Creoles, the Metis Indians, and the Lebanese.[11] The birth prevalence rate of Sandhoff disease is 1 per 309,000 births in non-Jewish populations.[12] Fourteen of the 125 LSD patients in Saudi Arabia (11.2%) presented with Sandhoff disease.[9]

Gaucher disease was confirmed in 8.1 % (7/86) in the study group. Worldwide, Gaucher disease has a birth prevalence of approximately 1.5 per 100,000 births; however, Ashkenazi Jews have a higher frequency of this disorder. In Saudi Arabia, Ozand *et al.* reported that 3 patients out of the 125 total patients seen with LSD had Gaucher disease. A retrospective study for LSDs from the United Arab Emirates (UAE) reported only four cases of Gaucher disease.[13] At SQUH, two siblings with type III Gaucher disease with a homozygous L444P/L444P mutation have been undergoing ERT for

eight and seven years, respectively. Although one of the children suffered from a severe progressive course of the disorder, he has shown remarkable improvement in terms of organomegaly and haematological parameters as a result of the treatment. His younger sibling was diagnosed and began ERT much earlier, at four months of age, and to date his mental development is improving. We observed that early treatment offers much better outcomes, except in the case of ophthalmoplegia, the course of which could not be altered.

Late infantile NCL was the single most common disease diagnosed in our cohort. A series of eleven cases had previously been reported, with most of the patients being from five families.[14] Late-infantile NCL, or Jansky-Bielschowsky disease (CLN2 type), was the most common type of NCL seen.[14] Over time, the number of cases had increased from nine to twenty families. In general, CLN2 remains the most frequently encountered type of NCL in Oman. However, other types of NCL are now diagnosed in Omani patients due to better availability of diagnostic tests. NCL is not an uncommon disease in Arab populations. Recently, Goldberg-Stern *et al.* reported two siblings of Israeli-Arab origin with CLN2 having a novel mutation.[15] Taschner *et al.* reported a patient with CLN3 from Morocco.[16] Sarpong *et al.* reported a large consanguineous Lebanese family with five affected siblings with a protracted course.[17] They had juvenile CLN associated with a novel CLN3 mutation (p.Y199*). Al-Muhaizea *et al.* reported on three families from Saudi Arabia with a variant of late infantile NCL, one of them having a novel mutation in the CLN6 gene.[18] Zelnik *et al.* described a different variant of CLN (CLN8) in a 10-year-old Israeli-Arab boy.[19]

MPS as a group constituted 23.2% of the total LSD cases. Most of the subtypes in our group were evenly distributed. However, MPS III was the most frequently noted subtype. Ozand *et al.* reported 19 patients with MPS IV out of 30 total patients with MPS. In Tunisia, the birth prevalence of MPS IVA was higher than in other communities (2.8:100,000). We treated one child with severe MPS I by ERT for 9 months in preparation for a BMT. This child no longer needs ERT after a successful bone marrow engraftment.

The proportion of consanguineous marriages in the Omani population in general is 56%.[20,21] About 24.1% of marriages were reported between first cousins, 11.8% between second cousins, and 20.4% of marriages were within specific tribal groups.[20] The proportion of consanguineous marriages in our patients' families was 87.5%, with most of those being first- and second-cousin marriages. Interestingly, 35% (30/86) of patients had a sibling with a similar illness at diagnosis. Only two patients in our series were diagnosed through high-risk screening. The importance of high-risk testing lies in prevention by premarital and prenatal screening, as well as in early initiation of treatment when available. It also helps in identifying those families who may benefit from appropriate genetic counselling, and it is strongly recommended to initiate such testing programmes for high-risk families.[22,23] High-risk testing programmes have now been established in Oman.

Conclusion

In this study, we report a combined birth prevalence of 1 in 4,700 live births for LSD in Oman. The limitation in our study is that it is retrospective and hospital-based. Additionally, we may have missed some cases which were not referred to SQUH. Therefore, this study likely underestimates the birth prevalence; diagnosis through a paediatric hospital setting such as ours will exclude the milder forms of the disease that may present in adulthood. There is also a bias due to missed diagnosis or death before diagnosis. Such factors cause an underestimation of the real prevalence. Oman's birth prevalence is less than that reported in other Gulf countries, such as Saudi Arabia. A testing programme for high-risk families in Oman has been successfully established at SQUH. A prospective study, along with a national screening programmes would help identify the exact birth prevalence of LSDs in Oman.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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