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RESEARCH REPORT

Inborn Errors of Metabolism in the United Arab Emirates: Disorders Detected by Newborn Screening (2011–2014)

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Abstract This study reports on the inborn errors of metabolism (IEM) detected by our national newborn screening between 2011 and 2014. One hundred fourteen patients (55 UAE citizens and 59 residents) were diagnosed during this period. The program was most comprehensive (tested 29 IEM) and universally applied in 2013, giving an incidence of 1 in 1,787 citizens. This relatively high prevalence resulted from the frequent consanguineous marriages (81.5%) among affected families. The following eight disorders accounted for 80% of the entities: biotinidase deficiency (14 of 55), phenylketonuria (11 of 55), 3-methylcrotonyl glycinuria (9 of 55), medium-chain acyl-CoA dehydrogenase deficiency (4 of 55), argininosuccinic aciduria, glutaric aciduria type 1, glutaric aciduria type 2, and methylmalonyl-CoA mutase deficiency (2 of 55 each). Mutation analysis was performed in 48 (87%) of the 55 patients, and 33 distinct mutations were identified. Twenty-nine (88%) mutations were clinically significant and, thus, could be included in our premarital screening. Most mutations were homozygous, except for the biotinidase deficiency. The *BTD* mutations c.1207T>G (found in citizens) and c.424C>A (found in Somalians) were associated with undetectable biotinidase activity. Thus, the high prevalence of IEM in our region is amenable to newborn and premarital screening, which is expected to halt most of these diseases.

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Introduction

Emirati citizens have diverse geoethnicities, which include ancestors from the Arabian Peninsula, Persia, Baluchistan, and East Africa. The culture is tribal and favors intra-tribal marriages. Related marriages are also common among most the expatriates, especially Palestinians and Pakistanis. Thus, rare autosomal recessive disorders are relatively common in the region and mostly result from homozygous mutations (Al-Jasmi et al. 2013; Al Shamsi et al. 2014).

A national neonatal screening program was established in the UAE in 1995. It aimed for early identification and treatment of IEM disorders to prevent morbidity and mortality. At first, it tested for phenylketonuria. Disorders of amino acid, organic acid, fatty acids, and biotinidase were added since 2011 and became comprehensive in 2013 (Al Hosani et al. 2014).

"Founder" mutations in cultures with high rates of consanguinity increase the frequency of autosomal recessive disorders (Woods et al. 2006). This problem explains the high incidence of certain IEM disorders in specific populations, such as the carnitine palmitoyltransferase type Ia P479L variant in Canadian Aboriginal people (Greenberg et al. 2009). Another example is the A421V variant in glutaryl-coenzyme A dehydrogenase (causing glutaric acidemia type I) in the Amish population (Biery et al. 1996). Genetic screening for certain mutations has been shown to halt diseases in specific populations (Strauss et al. 2012).

This study reports on IEM incidence rates and mutation spectrum identified by our newborn screening from 2011 to 2014. Its primary aim is to endorse preventive endeavors,

such as premarital counseling and genetic screening in order to mitigate these diseases in the community.

Methods

This study included all patients with IEM that were detected by newborn screening in the UAE from 2011 to 2014. Confirmatory work-up was done at Tawam Hospital (Al Ain City, Abu Dhabi) and was based on the guidelines of the American College of Medical Genetics (ACMG, http://www.ncbi.nlm.nih.gov/books/NBK5582).

Blood was collected in the hospital from all neonates at 48 h of age. Neonates who were sent home before 48 h were referred to designated centers for the newborn screening. The parents had legal right to refuse the test. Newborn screening samples are collected by nurses on Whatman 903 filter paper cards and analyzed by tandem mass spectrometry (API 3200™, HVD/Perkin Elmer). Sample preparations and instrument parameters were according to the manufacturers' recommendations. Biotinidase activity was analyzed using a spectrophotometric method (Cowan et al. 2010). The newborn screening coverage rate in 2010 was 95% (Al Hosani et al. 2014).

In 2011, only 12 disorders were included in the panel (Al Hosani et al. 2014). The program was expanded in 2013 to include disorders of amino acid metabolism (phenylketonuria, hyperphenylalaninemia, defects of biopterin cofactor biosynthesis and regeneration, tyrosinemias, argininosuccinic aciduria, citrullinemia (I and II), maple syrup urine disease, hypermethioninemia (homocystinuria due to cystathionine-β-synthase deficiency), and argininemia), disorders of organic acid metabolism (glutaric acidemia type I, 3-hydroxy 3-methylglutaryl-CoA lyase deficiency, isovaleric acidemia, 3-methylcrotonyl-CoA carboxylase deficiency, methylmalonyl-CoA mutase deficiency, methylmalonic acidurias due to cblA and cblB, methylmalonic acidemia with homocystinuria (cblC and cblD), beta-ketothiolase deficiency, propionic acidemia, multiple carboxylase deficiency due to holocarboxylase synthetase deficiency), disorders of fatty acid metabolism (medium-chain acyl-CoA dehydrogenase deficiency, long-chain hydroxyacyl-CoA dehydrogenase deficiency and trifunctional protein deficiency, very-long-chain acyl-CoA dehydrogenase deficiency, carnitine uptake defect, glutaric acidemia type II (multiple acyl-CoA dehydrogenase deficiency), carnitine palmitoyltransferase deficiency type 1, carnitine/acylcarnitine translocase deficiency and carnitine palmitoyltransferase type 2 deficiency), and biotinidase deficiency.

Live births were obtained from the National Bureau of Statistics (http://www.uaestatistics.gov.ae).

Results

The prevalence of IEM among citizens born in Abu Dhabi and other emirates between 2011 and 2014 is shown in Table 1. During this period, 55 patients were diagnosed based on positive newborn screening. The program was most comprehensive and universally applied in 2013. During this year, the incidence was 1 in 1,787 citizens. This relatively high rate resulted from frequent consanguineous marriages (81.5%) in the affected families. On the other hand, the incidence of metabolic disease in 2013 for residents was 1 in 3,132 (59,521 live births and 19 patients).

Five neonates were not included in Table 2: one had hyperphenylalaninemia associated with limb-girdle muscular dystrophy, two had nutritional vitamin B12 deficiency, and two had high tyrosine secondary to liver disease (transaldolase deficiency and mitochondrial DNA depletion). Seven additional citizen neonates (four in 2014 and three in 2011–2013) had positive screening but lost to follow-up before confirmatory testing. One of these newborns had low biotinidase level (14 units, cutoff value = 75 units), two had high 5-hydroxyisovaleryl carnitine/2-methyl-3-hydroxybutyryl carnitine (C5OH carnitine, 5.5 μM and 1.0 μM, cutoff value = 0.8 μM), one had high isovaleryl carnitine/2-methylbutyryl carnitine (C5 carnitine; 0.9 μM, cutoff value = 0.7 μM), and three had positive screening for organic acidemia, citrullinemia, and medium-chain acyl-CoA dehydrogenase deficiency. One more citizen infant had positive screening for tyrosinemia (↑succinylacetone) on a specimen that was collected at 6 months of age. Moreover, 16 resident infants with positive screening from 2011 to 2014 were lost to follow-up before the confirmatory testing.

Sixteen distinct entities (eight organic acidemias, four aminoacidopathies, three fatty acid oxidation disorders, and biotinidase deficiency) were identified in the 55 citizens with IEM (Table 2). The most common (80% of cases) disorders were biotinidase deficiency (14 of 55), phenylketonuria (11 of 55), 3-methylcrotonyl glycinuria (9 of 55), medium-chain acyl-CoA dehydrogenase deficiency (4 of 55), argininosuccinic aciduria, glutaric aciduria type 1, glutaric aciduria type 2, and methylmalonic aciduria (2 of 55 each) (Table 2).

Fourteen patients (25%) had immediate or extended family members affected with the disease. Screening family members for the disease, on the other hand, was not performed in 20 families (36%) due to various reasons that include parental refusal.

Molecular analysis revealed 33 mutations in 48 (87%) of the 55 patients (Table 3). The remaining seven patients (including one with hyperphenylalaninemia) did not have

Table 1 Prevalence of IEM among citizens born in Abu Dhabi and other emirates based on the national newborn screening program (2011–2014)

	Abu Dhabi			Other emirates			All emirates		
Years	Live births	No. of patients	Prevalences	Live births	No. of patients	Prevalences	Live births	No. of patients	Prevalences
2011	14,636	4	1 in 3,659	18,830	6	1 in 3,138	33,466	10	1 in 3,347
2012	15,173	10	1 in 1,517	18,827	5	1 in 3,765	34,000	15	1 in 2,267
2013[a]	15,576	9	1 in 1,730	18,389	10	1 in 1,839	33,965	19	**1 in 1,787**[b]
2014	16,032	5	1 in 3,206	18,595	6	1 in 3,099	34,618	11	1 in 3,147
2011–2014	61,417	28	1 in 2,193	74,641	27	1 in 2,764	136,049	55	1 in 2,474

[a] The program was most comprehensive and universally applied in 2013
[b] Bold values indicate high prevalence

Table 2 IEM disorders detected by the newborn screening (2011–2014)

	No. of patients	
	All nationalities	Citizens
Aminoacidopathies		
Phenylketonuria (10 ± 6 days)[a]	17	11
Hyperphenylanemia (21 days)	1	1
Dihydropteridine reductase deficiency (3 days)	1	1
Maple syrup urine disease (7 days)[a,b]	6	1
Citrullinemia type 1 (4 days)[b]	4	0
Citrullinemia type 2 (45 days)	1	0
Argininosuccinic aciduria (1–16 days)[a,b]	4	2
Arginase deficiency (21 days)	1	0
Organic acidemias		
3-Methylcrotonyl glycinuria (10 ± 6 days)	18	9
Glutaric aciduria type 1 (25 ± 9 days)	3	2
Propionic aciduria (10-40 days)[a,b]	3	1
Methylmalonic aciduria (11–16 days)[b]	3	2
Cobalamin B deficiency (3 days)[b]	1	1
Cobalamin C deficiency (9 ± 7 days)	2	1
Isovaleric aciduria (7 days)[b]	1	1
Beta-ketothiolase deficiency (22 days)	1	1
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (20 days)[a]	1	0
Fatty acid oxidation disorders		
Medium-chain acyl-CoA dehydrogenase deficiency (11 ± 7 days)	5	4
Carnitine deficiency (8–16 days)	2	1
Carnitine-acylcarnitine translocase deficiency (2 days)	1	0
Glutaric aciduria type 2 (9 ± 8 days)[b]	3	2
Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (11 days)	1	0
Other disorders		
Biotinidase deficiency (20 ± 8 days)[b]	34	14
Total	114	55 (48%)

Numbers in parentheses are age at the first visit to the metabolic service
[a] Some neonates with these disorders were diagnosed based on positive antenatal testing or family history before the newborn screening result
[b] Some neonates with these disorders were referred to the Metabolic Service with symptoms before the newborn screening result

Table 3 Mutations detected in the citizens (2011–2014)

Disorders	Gene	Nucleotide change	Amino acid change
Phenylketonuria	*PAH*	c.168+5G>C[a]	Splicing
		c.1066-11G>A	Splicing
		c.250G>T[b]	p.D84Y
		c.727C>T[b]	p.R243*
Dihydropteridine reductase deficiency	*QDPR*	c.49G>C[b]	p.G17R
Maple syrup urine disease	*DBT*	**c.1281+1G>T**	Splicing
Argininoosuccinic aciduria	*ASL*	**c.332G>A**[c]	p.R111Q
Propionic aciduria	*PCCB*	**c.1519C>T**	p.E507stop
Methylmalonic aciduria	*Mut*	c.2080C>T[b]	p.R694W
		c.1420C>T[b]	p.R474stop
Cobalamin B deficiency	*MMAB*	c.197-1 G>T	Splicing
Cobalamin C deficiency	*MMACHC*	c.271dupA	p.R91Kfs*14
3-Methylcrotonyl glycinuria	*MCCC1*	**c.1106C>G**	p.P369R
		c.694C>T	p.R232W
		c.89+2_89+34del	–
	MCCC2	**c.735dupC**[d]	p.V247Gfs*2
Beta-ketothiolase deficiency	*ACAT1*	**c.86_87dupTG**	p.E30Wfs*11
Glutaric aciduria type 1	*GCDH*	**c.242 C>T**	p.W81L
		c.427G>A	p.V143I
Isovaleric aciduria	*IVD*	**c.1193G>A**	p.R398Q
Glutaric aciduria type 2	*ETFDH*	c.1414G>A[b]	p.G472R
		c.807A>C	p.G269H
Medium-chain acyl-CoA dehydrogenase deficiency	*ACADM*	c.985A>G	p.K304E
		c.362C>T[b]	p.Y121I
Carnitine deficiency	*SLC22A5*	248G>T	p.R83L
Biotinidase deficiency[e]	*BTD*	c.476G>A[b]	p.S159N
		c.1330G>C	p.D444H
		c.1595C>T[b]	p.T532M
		c.968A>G	p.H323R
		c.1207T>G	p.F403V
		c.557G>A	p.C186Y
		c.1489C>T	p.P497S
		c.257T>C[b]	p.M86T

Mutations in bold are found only in citizens
[a] Eight patients from three tribes had the same mutations
[b] Mutations identified in citizens through the newborn screening
[c] Two patients from two tribes had the same mutations
[d] Two patients from two tribes had the same mutations. In addition, four mothers from two tribes had the same mutation and their newborns had abnormal C5OH analytes
[e] Ten (76%) of 13 patients had compound heterozygous mutations

mutational studies. Eleven (33%) mutations were reported only in Emirati citizens, and ten (30%) mutations were identified for the first time in Emiratis through the newborn screening (Table 3). Twenty-nine (88%) mutations were clinically significant; the remaining four (13%) mutations involved 3-methylcrotonyl glycinuria (Table 3).

Forty-four mutations were identified in residents (expatriates) (Table 4). Fifteen (34%) mutations were novel. Most mutations were homozygous, except for the biotinidase deficiency where compound heterozygotes were most common (Table 4). This finding reflects high frequency of the mutated alleles in our community. The most common

Table 4 Mutations detected in the expatriates (2011 to 2014)

Disorders	Gene	Nucleotide change	Amino acid change	Ethnicity
Phenylketonuria	*PAH*	c.842+1G>A	Splicing	Syria
		c.782G>A	p.R261Q	Egypt
		c.967_969delACA	p.T323del	Egypt
		c.165delT	p.F55Lfs	Syria
		c.226G>A	p.E76K	Sudan
		c.168+1G>A	Splicing	Palestine
Maple syrup urine disease	*BCKDHA*	**c.1227-1229 del CTC**	p.F409_410 delinsL	Sudan
		c.335T>C	p.L112P	Pakistan
	DBT	**c.634C>T**	p.Q212*	Yemen
	BCKDHB	**c.490G>A**	p.A164T	Jordan
Citrullinemia 1	*ASS1*	c.787G>A	p.V263M	Jordan
		c.535 T>C	p.W179R	Syria
		c.1168G>A	p.G390R	Pakistan
Citrullinemia 2	*SLC25A13*	c.1813C>T	p.R605X	Pakistan
Arginosuccinic aciduria	*ASL*	c.544C>G	p.R182G	Sudan
		c.971A>C	p.D324A	India
Arginase deficiency	*ARG1*	**c.130+1G>A**	Splicing	Syria
Propionic aciduria	*PCCA*	Deletion of exons and introns	–	Egypt
	PCCB	c.1540C>T	p.R514X	India
Methylmalonic aciduria	*Mut*	**c.1132G>T**	p. V378L	Pakistan
3-Methylcrotonyl glycinuria	*MCCC1*	**519bp deletion/1441G>T**	p.A481S	Sudan
		c.1267+3A>C	Splicing	Jordan
	MCCC2	**c.691A>T**	p.I231F	Iran
HMG-CoA lyase deficiency	*HMGCL*	**c.215_252+131del169**	Splicing	Jordan
Glutaric aciduria type 1	*GCDH*	**c.528C>G**	p.C176R	Pakistan
Cobalamin C deficiency	MMACHC	c.271dupA	p.R91Kfs*	Pakistan
		c.1A>G	p.M1	Pakistan
Carnitine deficiency	*SLC22A5*	c.1400 C>G	p.S467C	Afghanistan
Carnitine/acylcarnitine translocase	*SLC25A20*	**c.383T>A**	p.M128K	Iraq
Glutaric aciduria type 2	*ETFDH*	**c.122G>T**	p.R41L	Pakistan
Biotinidase deficiency	*BTD*	c.626G>A	p.R209H	Egypt
		c.1368A>C	p.Q456H	Palestine
		c.380C>T	/p.P127L	Australia
		c.1420G>T	p.E474X	Iraq
		c.470G>A	p.R157H	Syria
		c.557G>A	p.C186Y	Pakistan
		c.1330G>C	p.D444H	Panethnic[a]
		c.968A>G	p.H323R	India
		c.476G>A	p.S159N	India
		c.1595C>T	p.T532M	Syria, Morocco, Yemen
		c.424C>A	p.P142T	Somalia
		c.476G>A	p.S159D	India
		c.922A>C	p.M308L	India
		c.1489C>T	p.P497S	Egypt

Mutations in bold are novel

[a] Oman, Pakistan, Palestine, Morocco, and Australia

Table 5 Biotinidase activity as a function of genotype

	Genotype	Biotinidase activity (unit/L)
Homozygous mutations	**c.424C>A**/c.424C>A	0
	c.470G>A/c.470G>A	0.8 ± 0 (n = 2)
	c.557G>A/c.557G>A	1.4
	c.1330G>C/c.1330G>C	3.7 ± 0.6 (n = 4)
Compound heterozygous mutations	**c.1207T>G**/c.1330G>C	0
	c.1489C>T/c.1330G>C	1.3
	c.476G>A/c.1330G>C	1.9
	c.1595C>T/c.1330G>C	2.0
	c.1420G>T/c.1330G>C	2.0
	c.1368A>C/c.1330G>C	2.2
	c.1595C>T/c.1330 G>C	2.3 ± 0.4 (n = 4)
	c.557G>A/c.1330G>C	2.6 ± 0.6 (n = 2)
	c.626G>A/c.1330G>C	3.1
	c.968A>G/c.1330G>C	3.8
	c.257T>C/c.1330G>C	3.1
	c.1489C>T/c.968A>G	2.1
	c.1595C>T/c.968A>G	2.5
	c.476G>A/c.968A>G	3.0
	c.476G>A/c.922A>C	2.8

Reference values for the biotinidase activity range from 3.5 to 13.8 unit/L; values between 1.5 and 3.4 units/L correspond to milder variants or carrier states (Mayo Clinic Medical Laboratories). Mutations in bold are associated with activities <1.5 unit/L

disorder among residents was biotinidase deficiency (20 of 59, Table 2). Other frequent disorders were 3-methylcrotonylglycinuria (9 of 59), phenylketonuria (6 of 59), maple syrup urine disease (5 of 59), citrullinemia type 1 (4 of 59), propionic acidemia (2 of 59), and argininosuccinic aciduria (2 of 59) (Table 2).

Five (22%) of the 23 disorders in Table 2 were identified only in citizens, while six (26%) of the 23 disorders were identified only in residents. Fifteen (83%) of the 18 patients with 3-methylcrotonyl glycinuria were tested for carnitine level (free and total) (Table 2). Eleven (73%) of these patients had secondary carnitine deficiency and received supplementation.

Eight maternal diseases were detected through the newborn screening. Five neonates (four citizens and one resident) had positive screening for the C5OH analyte due to maternal 3-methylcrotonyl-CoA carboxylase deficiency. In addition, three neonates (one citizen and two residents) had abnormal C3 analyte levels due to maternal vitamin B12 deficiency.

Biotinidase activities as a function of genotype are shown in Table 5. Five (26%) of the 19 mutations were associated with profound biotinidase deficiency (enzyme activity <1.5 unit/L). The mutations c.424C>A (found in Somalians) and c.1207T>G (found in citizens) were associated with undetectable enzyme activity (Table 5).

In 2011–2014, the overall time between birth and first clinical visit for infants with a true-positive or a false-positive screening was 19 ± 15 days (n = 149, median 14 days, range 1–85 days). In 2014, the time between sample collection and reporting true-positive result was 2.5 ± 1.4 days (n = 23). The time between reporting true-positive result and first clinical visit was 3.2 ± 1.8 days (n = 21).

It is worth noting that in 2011–2014, 9 (8%) of the 114 infants with IEM presented before the newborn screening result and 5 (4%) had no testing at birth due to various reasons (samples were processed subsequently at the first clinic visit) (Table 6). Most of these patients had unfavorable outcome (Table 6).

Table 7 shows examples of analyte-based true-positive and false-positive cases in 2014. This type of analysis aimed to refine absolute cutoff values for the analyte markers.

Discussion

There were 136,049 live births (citizens) from all emirates in 2011–2014. Fifty-five infants were diagnosed with IEM during this period, giving a prevalence of 1 in 2,474 (Table 1). Sixteen patients (29%) had aminoacidopathies, 18 (33%) had

Table 6 Infants with IEM who presented to the metabolic service before the newborn screening results ($n = 9$) or had no testing at birth ($n = 5$) in 2011–2014

Disease	Comments
Tyrosinemia	Newborn screening was not done. Infant presented at 6 months of age with liver disease. Parents refused early therapy; nitisinone and tyrosine-free diet were started at 1 year of age
Maple syrup urine disease	Newborn screening was not done. Infant presented at 11 days of age with poor feeding. Diagnosis was made at 3 weeks of age and he died shortly thereafter
Maple syrup urine disease	Family refused newborn screening. Diagnosis was made at 10 days of age. Patient received liver transplantation
Citrullinemia type I	Hyperammonemia (1,985 mmol/L) was detected on the first day of age. Dialysis was started on the second day of age. Good clinical outcome
Citrullinemia type I	Infant presented on the third day of age and died on the seventh day
Arginosuccinic aciduria	Infant presented on the third day of age with sepsis-like illness. Diagnosis was made in the third week of age. Poor clinical outcome
Propionic aciduria	Newborn screening was not done. Patient died at 2 years of age
Propionic aciduria	Patient had positive family history. Diagnosis was made clinically at 10 days of age
Propionic aciduria	Patient presented at 2 day of age with irritability and died at 15 days of age
Methylmalonic aciduria	Patient presented on the fourth day of age with hypoglycemia and thrombocytopenia. Good clinical outcome
Methylmalonic aciduria	Patient presented on the third day of age with hyperammonemia. Good clinical outcome
Isovaleric aciduria	Diagnosis was made at birth based on positive family history. Good clinical outcome
Glutaric aciduria type 2	Patient presented on the second day of age and died on the seventh day of life before the newborn screening result
Biotinidase	Newborn screening was not done. Patient presented with seizure

Five neonates missed the newborn screening; one family declined the test and four families did not show up for the appointment

Table 7 Analyte-based true-positive and false-positive cases in 2014

	True positive		False positive	
Primary analyte (cutoff values)	No. of patients	Analyte value	No. of patients	Analyte value
Biotinidase (=75 U)	7	25 ± 4	8	33 ± 8 ($p = 0.094$)
5-Hydroxyisovaleryl carnitine (>0.8 μM)	4	4.2 ± 1.6	4	5.14 ± 5.6 ($p = 0.686$)
Phenylalanine (=120 μM)	4	575 ± 105	1	193
Propionyl carnitine (=7.0 μM)	2	9.8 ± 3.2	3	9.7 ± 0.6
Octanoylcarnitine (=0.40 μM)	1	3.7	0	–
Leucine (=300 μM)	1	1,363	0	–
Citrulline (=40 nM)	1	340	1	84
Isovaleryl carnitine (=0.7 μM)	0	–	4	1.5 ± 0.7

True-positive and false-positive cases are based on biochemical and/or genetic conformation following ACMG guidelines. Patients' values (mean ± SD, n) are based on available data
The mothers of neonates with false-positive 5-hydroxyisovaleryl carnitine screening had normal results
The p-values are nonparametric (2 independent samples) Mann–Whitney test

organic acidemias, 7 (13%) had fatty acid oxidation disorders, and 14 (25%) had biotinidase deficiency (Table 2). In Saudi Arabia, 27,624 newborns were screened at birth and 20 cases were identified, yielding a frequency of 1:1,381 (Rashed et al. 1999). In a study from Qatar, 25,214 neonates were screened at birth, and 19 patients were diagnosed with IEM, giving an incidence of 1 in 1,327 (Lindner et al. 2007). Two infants (11%) had biotinidase deficiency, 6 (32%) had MCAD, 1(5%) had carnitine deficiency, 7 (37%) had aminoacidopathies and urea cycle disorders, and 3 (16%)

had organic acidemia (Rashed et al. 1999). Thus, the rate observed in this study (Table 1) is consistent with the high incidence of IEM disorders in our region (Rashed et al. 1999; Lindner et al. 2007).

Homocystinuria is considered one of the most prevalent disorders in Qatar. Even though homocystinuria is poorly detected by using methionine as the primary indicator, they have detected two patients using this method (Lindner et al. 2007). Homocystinuria was not detected in our studied population.

For comparison, in North Carolina, 944,078 neonates were screened in 1997–2005; 219 patients were diagnosed with IEM, giving an incidence of 1 in 4,310 (Frazier et al. 2006). Ninety-nine infants (45%) had fatty acid oxidation disorders, 62 (28%) had aminoacidopathies, and 58 (26%) had organic acidemias (Frazier et al. 2006). In Denmark, 504,049 neonates were screened in 2002–2010; 114 were diagnosed with IEM, giving an incidence of 1 in 4,422 (Lund et al. 2012). In Singapore, 177,267 neonates were screened in 2006–2014; 56 patients were diagnosed with IEM, giving a detection rate of 1 in 3,165 (Lim et al. 2014). Twenty-three infants (41%) had organic acidemias, 23 (41%) had fatty acid oxidation disorders, and 10 (18%) had aminoacidopathies (Lim et al. 2014).

Another problem featured in this study is the high level (81.5%) of parental consanguinity (intra-tribal marriages) among the families of affected infants. Consistently, 14 (25%) of the 55 patients had other family members affected with the same disorder. Interestingly, 29 mutations were responsible for the clinically significant disorders among citizens (Table 3). It is worth emphasizing that "founder" mutations in our culture, which favors consanguinity marriages, are amenable to premarital counseling and genetic screening. As previously shown in other nations (Greenberg et al. 2009; Biery et al. 1996; Strauss et al. 2012), screening for certain mutations (e.g., the clinically significant mutations in Table 3) is expected to halt most of the identified IEM diseases (Table 2). This cost-effective approach needs to be combined with effective family counseling, aiming at improving public awareness about transmission of genetic diseases and endorsing intertribal marriages.

More than 165 mutations have been previously identified in the biotinidase gene; most of them result in profound biotinidase deficiency (activity <10% normal), except for the c.1330G>C mutation that causes a partial deficiency (Procter et al. 2013; Li et al. 2014; Ohlsson et al. 2010; Hymes et al. 2001; Gannavarapu et al. 2007). A high incidence of partial biotinidase deficiency has been reported in the Greek population (Thodi et al. 2013). Profound biotinidase deficiency, on the other hand, has been reported in the Somalian population (e.g., the presence of c.424C>A mutation with zero enzyme activity in Somalians; Tables 4 and 5) (Sarafoglou et al. 2009). All patients shown in Table 5 were treated with biotin (Gannavarapu et al. 2007).

Cardiomyopathy has been reported in children with carnitine deficiency associated with 3-methylcrotonyl-CoA carboxylase (3-MCC); and carnitine supplementation has been recommended for these patients (Arnold et al. 2008). In this study, there were 11 patients who had 3-MCC deficiency with secondary carnitine deficiency and received supplementation (see Results).

The advantages of newborn screening have been emphasized in several studies (Therrell et al. 2014; Mak et al. 2013). As shown in Table 6, treatment based on positive newborn screening prevents serious and costly complications. At least half of the identified patients in this study required highly specialized managements of a widely variable annual cost. For example, the cost of managing a patient with citrullinemia is about $8,000 per year (based on reviewing local records). The corresponding value for initial stabilization of infants presenting with symptoms is about $40,000 (an average estimation of the local cost). Similarly, the serious complications of medium-chain acyl-CoA dehydrogenase can be simply prevented by avoidance of fasting and of biotinidase deficiency by biotin supplementation.

There were 23 neonates (16 residents and 7 citizens) with a positive screening who were lost to follow-up. These cases are a serious concern to the program and require national health policies to overcome.

The current screening program should be improved to include the detection of homocystinuria using total homocysteine on dried blood spots by tandem mass spectrometry. Moreover, screening for classical galactosemia should be implemented using galactose-1-phosphate uridylyltransferase activity.

The magnitude of problems caused by IEM and their potential simple solutions justify campaigning for effective premarital counseling and genetic screening. Our premarital program needs to be integrated with the newborn screening in order to better mitigate IEM disorders in the community.

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Compliance with Ethical Guidelines

Authors' Contributions

FAJ and AKS developed the concept of the study and wrote the first and final versions of the manuscript. AS, JH, and SA collected the patients' data. All authors read and approved the final manuscript.

Conflict of Interest

Competing Interests

Aisha Al Shamsi, Jozef Hertecant, Sania Al Hamad, and Abdulkader Souid declare that they have no conflict of interest. Fatma Al-Jasmi has received a speaker honorarium from Genzyme and Shire.

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