

Spectrum of Inborn Errors of Metabolism in Jordan: Five Years Experience at King Hussein Medical Center

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ABSTRACT

Objective: To describe the different types, and frequencies of inborn errors of metabolism in the Pediatric Metabolic Genetics Clinic at King Hussein Medical Center, Amman, Jordan.

Methods: A retrospective review of the medical records of patients attending the metabolic genetics clinic who were diagnosed to have an inborn error of metabolism over the last five years (Jan 2005-Jan 2010) was conducted. The following data were recorded, age, gender, diagnosis, consanguinity of parents, and the presence of affected family members or relatives.

Results: A total of 212 patients were included in the study, 107 were males and 105 were females with a male to female ratio of 1:1. The mean age of patients at diagnosis was 11.8 ± 11.1 months (range 1-50 months). Fifty seven (27.8%) patients had aminoacidopathies of whom 24 (11.3%) had tyrosinemia, 51 (24.1%) patients had organic acidemias of whom 14 (6.6%) had propionic acidemia. Twenty five (11.8%) had lysosomal storage diseases, 21 (9.9%) patients had glycogen storage disease. Seventeen had dyslipidemias, seven (8%) had peroxisomal disorders, four (1.9%) had galactosemia, and 28 (13.2%) had other diagnoses. Parental consanguinity was noted in 137 out of 151 families, and 79 of 151 families (54%) had another affected family member.

Conclusion: Patients with inborn errors of metabolism are becoming increasingly diagnosed. Tyrosinemia is the most common of the aminoacidopathies, whereas propionic acidemia is the commonest of the organic acidemias. Due to the difficulties and delay in diagnosing these diseases, newborn screening is highly recommended for early intervention and counselling.

Key words: Jordan, Inborn errors, Metabolism, Pediatric.

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Introduction

Inborn errors of metabolism (IEM) are caused by genetic defects which result in abnormalities in the synthesis or catabolism of proteins, carbohydrates, fats or other metabolites,⁽¹⁾ while the diseases are individually rare, they collectively account for a significant proportion of illness, particularly in children.

They present clinically in a variety of ways, involving virtually any organ or tissue of the

body, and accurate diagnosis is important both for treatment and prevention of disease in other family members.⁽²⁾

The increasing application of new technologies such as tandem mass spectrometry (MS-MS) to newborn screening allows early identification of inborn errors of metabolisms. The disorders detected by tandem mass spectrometry generally include aminoacidopathies, urea cycle disorders, organic acidurias, and fatty acid oxidation disorders.⁽³⁾

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Table I: Types and frequencies of IEM among the study group

Disease category	Disease	Number	%
Aminoacidopathies	Tyrosinemia	24	11.3
	Phenylketonuria	17	8
	Maple syrup urine disease	13	6.1
	Homocysteinurea	3	1.4
Organic acidemias	Propionic acidemia	14	6.6
	Methylmalonic acidemia	6	2.8
	HMG-Co enzyme a lyase defficiency	2	0.9
	undiagnosed	29	13.7
Lysosomal storage diseases	Mucopolysaccharidosis	13	6.1
	Niemann-Pick disease	6	2.8
	Gaucher disease	4	1.9
	Tay-Sachs disease	2	0.9
Carbohydrate disorders	Glycogen storage diseases	21	9.9
	Galactosemia	4	1.9
Dyslipidemias		17	8
Peroxisomal disorders		7	3.4
Urea cycle disorder		2	0.9
Primary lactic acidosis		5	2.4
others		23	10.9
Total		212	100

This study was conducted to describe the different types, and frequencies of inborn errors of metabolism in the Pediatric Metabolic Genetics Clinic at King Hussein Medical Center, Amman, Jordan.

Methods

Review of the medical records of patients attending the metabolic genetics clinic who were diagnosed to have an inborn error of metabolism over the last five years (2005-2010) was carried out. Ages of patients ranged from one week to 18 years. These patients currently are seen only in the pediatric metabolic clinic. The following data were recorded: age, gender, diagnosis, age at diagnosis, consanguinity of parents, and the presence of affected family members or relatives.

Our data relate only to conditions which cause a clinical disease state. In all cases, the clinical findings and response to therapy, in which therapy is possible, were consistent with the stated diagnosis.

Laboratory tests used for the initial diagnosis and detection of diseases included the following: full blood counts, liver function tests, renal function tests, serum electrolyte profile, blood glucose, blood gases, ammonia, lactate levels, and urine ketones which were performed on all patients at the time of presentation. Quantitative plasma amino acid analyses, urine organic acids,

acylcarnitine profile by gas chromatography-mass spectrometry, very long-chain fatty acids for the diagnosis of peroxisomal disorders. Specific enzyme assays were also performed for some diseases, including galactosemia, glycogen storage diseases, lysosomal storage diseases, when indicated. Due to lack of tandem mass spectrometry and enzyme assay, many tests were sent to specialized laboratories outside the country.

Results

A total 212 patients were included in the study, 107 were males and 105 were females with a male to female ratio of 1:1. The mean age of patients at diagnosis was 11.8±11.1 months (range 1-50 months).

The types and frequencies of different diseases are shown in Table I.

Fifty-seven (26.9%) patients had aminoacidopathies of whom 24 (11.3%) had tyrosinemia, 17 (8%) had phenylketonuria, 13 (6.1%) had maple syrup urine disease and three had homocysteinuria (1.4%).

Fifty one (24.1%) patients had organic acidemias of whom 14 (6.6%) had propionic acidemia, 6 (2.8%) methylmalonic academia, and 2 (0.94%) had HMG Co layase deficiency. Twenty nine (13.7%) cases the exact type was not found although they preseneted with acidotic

breathing with or without encephalopathy and their blood gases was showing wide anion gap metabolic acidosis, high ammonia and lactate but the samples for specific diagnosis such as organic acid chromatography in urine were mostly sent while the patients are on nothing per mouth but on intravenous fluid.

Two (0.94%) patients were found to have urea cycle defects, 5(2.4%) had primary lactic acidosis. Twenty five (11.8%) had lysosomal storage diseases 13(6.1%) had mucopolysaccharidosis, 4 (1.9%) had Gaucher, 6 (2.8%) Niemann-Pick disease and 2(0.9%) had Tay-Sachs disease. Twenty one (9.9%) patients had glycogen storage disease. Seventeen (8%) had dyslipidemias, seven (3.3%) had peroxisomal disorders. Four (1.9%) had galactosemia, and 23(10.9%) had other diagnoses such as fructose 1.6 diphosphatase deficiency, congenital glucose galactose malabsorption, Fanconi Bickel syndrome and fatty acid oxidation defects.

One hundred fifty two (71.6%) of our cases had aminoacidopathies, organic acidemias, carbohydrate disorders, lipid and fatty acid oxidation defects which were amenable to treatment as they could receive specific dietary or drug therapy. One hundred thirty seven (90.7%) out of 151 families of these patients whose consanguinity was known were consanguineous $P=0.05$, and 79 (52%) of patients gave family history of similar illness (sibling death or other affected siblings).

Discussion

Inborn errors of metabolism (IEM) constitute a highly heterogeneous category of rare diseases, representing a relevant cause of morbidity and mortality in childhood.⁽⁴⁾

The number, complexity, and variety of clinical presentation of metabolic disorders present a significant challenge to the practicing pediatrician. Yet, in many cases, prevention of death or permanent neurologic sequelae in patients with these disorders is dependent on early diagnosis and institution of appropriate therapy.⁽⁵⁾ It is therefore very important to be familiar with the major signs and symptoms of these diseases and with the initial laboratory workup necessary to arrive at an initial diagnosis, as early suspicion and initiation of appropriate investigations by the referring physician is the

most significant contributor to prompt diagnosis⁽⁶⁾ as well as initiation of screening programmes that include the most common inborn metabolic diseases in our country.

This is the first study in Jordan with attempts to collect data on the pattern, and diagnosis of IEM. The diagnosed cases represent patients who were referred to KHMC, with the suspicion to have IEM, cases who attended the outpatient and emergency department, and cases of families with IEM. These figures would just represent a small proportion of the cases as there is no newborn screening program so far in the country, and because of the different sectors running the health care system in the country. Currently, there are no guidelines for paediatricians on the abnormalities to look for and the indications for referral of such cases. However, an increase in the diagnosis has been observed due to the increased awareness on the part of the pediatricians over the last few years.

The incidence of metabolic diseases in Jordan is not known although the incidence in some Arab countries was 1:1327 in Qatar,⁽⁷⁾ 1:1,381 in Saudi Arabia,⁽⁸⁾ and 1:1555 in Oman,⁽⁹⁾ which could represent our type of population with high rates of consanguinity. On the other hand, figures from the Caucasian population showed an incidence of 1: 2500 live births in British Columbia⁽¹⁰⁾ and 1:2517 in Germany⁽⁷⁾ and the incidence was 1:2758 in Italy.⁽⁴⁾

Diagnosis of metabolic disorders depends on a careful history, detailed clinical examination and request of relevant investigations. Regarding the diagnosis in our cohort, some of our patients were clinically diagnosed due to the limited number of pediatricians with expertise in inherited metabolic disorders, in addition to shortage of well-equipped laboratory facilities. The mean age of patients at diagnosis was (11.8 ± 11.1) months which shows a relatively late age at the diagnosis of these patients.

As shown in table I, the most frequent disease category was the aminoacidopathies in contrast to studies in Oman and Italy showing the lysosomal storage diseases to be the commonest.^(4,9)

Of the aminoacidopathies, tyrosinemia constituted 11.3% (24/212 patients) which contrasts with other studies showing higher prevalence of phenylketonuria and maple syrup

urine disease.^(11,12) Phenylketonuria was diagnosed in 17 cases that were relatively easy to treat with good outcome, whereas the thirteen patients with maple syrup urine disease presented relatively later.

In the organic acidemias, propionic acidemia was the most common and constituted 27% (14/51 patients) although methylmalonic acidemia was more common in other parts of the world.⁽¹³⁻¹⁵⁾

Lysosomal storage diseases were diagnosed in 25 (11.8%) patients and unfortunately have no specific treatment in the country so far. Glycogen storage diseases occurred in 21 (9.9%) patients, all apart from 5 (2.4%) patients had type I disease, 3 (1.4%) patients had type III, and 1 (0.5%) patient each for type II and I (0.5%) type IV.

Unfortunately, only 152 (71.6%) of our cases; aminoacidopathies, organic acidemias, carbohydrate disorders, lipid and fatty acid oxidation defects were amenable to treatment as they could receive specific dietary or drug therapy, whereas some diseases like lysosomal storage diseases and peroxisomal diseases received only supportive and symptomatic treatment. Some of the latter diseases will benefit from enzyme replacement therapy and some may benefit from bone marrow or liver transplantation which, hopefully, should be available for these patients in the near future.

Parental consanguinity was found in 137 (90.7%) out of 151 families whose consanguinity was known which is similar to figures from Oman.⁽¹¹⁾ These figures are much higher than the general population figures in Jordan,⁽¹⁶⁾ and some other Arab countries where the consanguinity is around 50%.^(9,16) And this would be an important contributing factor in these illnesses.

Family history of similar illness (sibling death or other affected siblings) was present in 79 (52%) out of 151 families in whom this information was known.

To conclude, IEM constitute a significant number of chronic pediatric patients, late diagnosis is common and would have significant untoward effects on the prognosis, as well as health costs.

As shown by a number of researchers,^(18,19) newborn screening would diagnose a significantly higher number of cases, at an earlier

age, with significantly more favourable prognosis and this highlights the importance of screening. It is therefore, very important to start a screening program in the country, as this will help to early diagnose higher number of patients, and this in turn will be very helpful for early intervention and counselling.

Conclusion

Patients with inborn errors of metabolism are becoming increasingly diagnosed. Tyrosinemia is the most common of the aminoacidopathies, whereas propionic acidemia is the commonest of the organic acidemias. Due to the difficulties and delay in diagnosing these diseases, newborn screening is highly recommended for early intervention and counselling.

References

1. **Arn P, Valle D, Brusilow S.** Inborn errors of metabolism: not rare, not hopeless. *Contemp Pediatr.* 1988; 5: 47-63.
2. **Clarke J.** General principles, In: A clinical guide to inherited metabolic disease, 3rd edition. Cambridge university press; 2006:1-27.
3. **Wilcken B, Wiley V, Hammond J, Carpenter K.** Screening newborns for inborn errors of metabolism by tandem mass spectrometry. *N Engl J Med* 2003 Jun 5; 348(23):2304-23012.
4. **Dionisi-Vici C, Rizzo C, Burlina A, et al.** Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. *J Pediatr* 2002 Mar; 140(3): 321-237.
5. **Burton B.** Inborn Errors of Metabolism in Infancy: A Guide to Diagnosis. *Pediatrics* 1998;102:e69
6. **Glass H, Feigenbaum A, Clarke J.** A study on the nature of genetic metabolic practice at a major pediatric referral centre. *J Inherit Metab Dis* 2006; 29:175-8.
7. **Lindner M, Abdoh G, Fang-Hoffmann J.** Implementation of extended neonatal screening and a metabolic unit in the State of Qatar: developing and optimizing strategies in cooperation with the Neonatal Screening Center in Heidelberg. *J Inherit Metab Dis* 2007 Aug; 30(4): 522-529.
8. **Rashed M, Rahbeeni Z, Ozand P.** Application of electrospray tandem mass spectrometry to neonatal screening. *Semin Perinatol* 1999 Apr; 23(2):183-93.
9. **Joshi SN, Hashim J, Venugopalan P.** Pattern of inborn errors of metabolism in an Omani population of the Arabian Peninsula. *Ann Trop Paediatr* 2002 Mar; 22(1):93-6.

10. **Applegarth D, Toone J, Lowry R.** Incidence of Inborn Errors of Metabolism in British Columbia, 1969-1996. *Pediatrics* 2000;105:e10
11. **Joshi SN, Venugopalan P.** Clinical characteristics of neonates with inborn errors of metabolism detected by Tandem MS analysis in Oman. *Brain Dev* 2007 Oct;29(9):543-6
12. **Velázquez A, Vela-Amieva M, Cicerón-Arellano I, et al.** Diagnosis of inborn errors of metabolism. *Arch Med Res* 2000; 31(2):145-150.
13. **Yang Y, Yao Z, Song J, et al.** Outcome of Organic Acidurias in China. *Ann Acad Med Singapore* 2008;37(Suppl 3):120-2
14. **Wasant P, Svasti J, Srisomsap C, Liammongkolkul S.** Inherited metabolic disorders in Thailand. *J Med Assoc Thai* 2002 Aug; 85 Suppl 2: S700-S709.
15. **Mohamed S, El-Khodary H, Khalifa N, et al.** Pattern of metabolic disorders presenting to pediatric and metabolic clinics in developing countries. *Research Journal of Medicine and Medical Sciences* 2009; 4(1): 14-19.
16. **Khoury S, Massad D.** Consanguineous marriage in Jordan. *Am J Med Genet* 1992; 43:769-75.
17. **El-Hazmi M, Al-Swailem A, Warsy A, et al.** Consanguinity among the Saudi Arabian population. Consanguinity in different regions of Saudi Arabia. *J Med Genet* 1995; 32: 623-626.
18. **Schulze A, Lindner M, Kohlmüller D, et al.** Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. *Pediatrics* 2003; 111(6 Pt 1):1399-406.
19. **Wilson C, Kerruish NJ, Wilcken B, et al.** The failure to diagnose inborn errors of metabolism in New Zealand: the case for expanded newborn screening. *N Z Med J* 2007 Sep 21; 120(1262):U2727.