Original Article

Demographic and clinical characteristics of the children with aminoacidopathy in Isfahan Province, Central Iran in 2007–2015

Reza Najafi[1,2], Mahin Hashemipour[3], Omid Yaghini[4], Fatemeh Najafi[5], Amirsalar Rashidianfar[6]

[1]Department of Pediatric Endocrinology and Metabolism, Ilam University of Medical Sciences, [5]Internal and Surgical Nursing, Ilam University of Medical Sciences, Ilam, [2]Endocrine and Metabolism Research Center, University of Medical Sciences, [3]Child Growth and Development Research Center, Isfahan University of Medical Sciences, [4] Department of Pediatric Neurology, University of Medical Sciences, Isfahan, Iran, [6]Medical Student, University of New South Wales, Sydney NSW 2052, Australia

ABSTRACT

Context: Aminoacidopathies refer to defects in protein synthesis pathways which result in a range of biochemical disorders and clinical presentations. The enzyme defects in intermediate metabolic pathways lead to accumulation of one or more amino acids or metabolites. Despite higher prevalence rates, screening infants for inherited metabolic disorders is not run in many Middle East countries. **Aim:** This research is part of a larger study of inherited metabolic disorders to characterize and measure the prevalence of aminoacidopathies. **Settings and Design:** Cross-sectional study in the population aged 0–17 years old in Isfahan province of Iran, 2007–2015. **Subjects and Methods:** Demographic characteristics, history of disease, development of clinical condition and socioeconomic status were obtained from interviews as well as patient records of pediatric tertiary referral hospitals and metabolic disorders centers. **Statistical Analysis Used:** SPSS qualitative and quantitative analysis. **Results:** The incidence rate of aminoacidopathies was derived to be 9/100,000 live births. The frequency of consanguineous marriages in this group of the patients was 89.2%. Of the patients with aminoacidopathies, 76.6% required hospitalization with tyrosinemia having the highest rate overall (>10 times). The most prevalent symptoms in this group of patients were developmental disorders and convulsions while half presented with growth disorders during follow-up. Of the 35.5% patients, who died at various ages, one-third was in the maple syrup urine disease subgroup. **Conclusion:** Although metabolic disorders are identified as rare diseases, they are more prevalent in the studied population of Isfahan.

Key words: Aminoacidopathy, consanguinity, early detection

Introduction

Inherited metabolic disorders are a group of heterogeneous and complex monogenic diseases which are caused by inadequate enzymes or cofactors activity in metabolic pathways. This leads to deficiency or accumulation of specific metabolite such as proteins, carbohydrates, fats, or complex molecules.[1] They may involve any organ, and clinical outcome of these disorders are usually severe which can lead to significant mortality and morbidity. The age of clinical presentation varies depending on the type of disorder, and the onset and severity are affected by environmental factors.[2,3]

Aminoacidopathies refer to defects in protein synthesis pathways that result in a variety of biochemical abnormalities

Corresponding Author: Prof. Mahin Hashemipour, Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: hashemipour@med.mui.ac.ir

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.190556

Cite this article as: Najafi R, Hashemipour M, Yaghini O, Najafi F, Rashidianfar A. Demographic and clinical characteristics of the children with aminoacidopathy in Isfahan Province, Central Iran in 2007-2015. Indian J Endocr Metab 2016;20:679-83.

and clinical presentations.[4] These disorders are mainly inherited in an autosomal recessive fashion and are particularly prevalent in countries where consanguineous marriages are prevalent.[5] The enzyme defects in intermediate metabolic pathways lead to accumulation of one or more amino acids or metabolites which are identified using laboratory methods such as high-performance liquid chromatography.[6]

The diagnosis is mainly made through clinical suspicion. The clinical presentations of aminoacidopathies are often nonspecific, and these disorders are usually underdiagnosed. The diagnosis is confirmed by laboratory tests and analysis of amino acid data. However, regardless of clinical signs and symptoms, many of the aminoacidopathies are diagnosed during infancy using tandem mass spectrometry (MS/MS)[7] which leads to earlier clinical intervention and improved clinical outcomes.[8]

Screening infants for inherited metabolic disorders are not run in many Middle East countries. The studies conducted in some Middle East countries have demonstrated a higher prevalence of inherited metabolic disorders compared with other regions worldwide.[9]

Subjects and Methods

This research is part of a larger cross-sectional study of inherited metabolic disorders in the population aged 0–17 years old in Isfahan province of Iran between 2007 and 2015. Demographic characteristics, history of disease, developmental, and educational status as well as general and clinical condition were obtained from patient records of metabolic disorders centers and pediatric tertiary referral hospitals (Imam Housayn, Alzahra, Amin). The data needed for the completion of questionnaires developed for this purpose was gathered by a resident of pediatric endocrinologist and a trained nurse through telephone and interview with parents.

Within the 8 years, a period of 2007–2016, 5100 patients with suspected inherited metabolic disorders underwent metabolic tests with the inclusion criteria of special clinical symptoms or known family history of metabolic diseases. The diagnosis was confirmed by Wagnerstibbe Laboratory of Metabolic Diseases located in Germany, using enzymes and metabolites in biological fluids samples. The exclusion criteria were a lack of cooperation and/or parental consent and inadequate laboratory test results. The study protocol was approved by Isfahan Metabolic Research Center, affiliated with Department of Pediatric Endocrinology of Isfahan University of Medical Sciences.

Consanguineous marriage is referred to marriage between two people who are related through bloodline and carry similar genes with identical physical and chemical structure. First, cousin marriages are referred to marriages between first degree cousins [Table 1].[10] Similar to the study by Carlo *et al*., the incidence proportion of the disease was derived by dividing the number of live births obtained from Department of Census and Statistics of Isfahan Province to the number of the patients diagnosed with the disease.[11] Qualitative and quantitative data analysis was further performed using SPSS 22 software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY).

Results

Of the 5100 screened patients, 392 had inherited metabolic disorders, of whom 55 patients suffered from aminoacidopathies [Table 2]. Notably, the patients with phenylketonuria were excluded from the study because their data were not presented by health center for analysis.

The incidence rate of aminoacidopathies was 9/100,000 (1/10,989) live births. The biggest subgroup in Isfahan province belonged to tyrosinemia (1/21,509 live births).

Table 1: Family kinship classification and fraction of shared genes

Type	Degree of kinship	Shared genes	Inbreeding coefficient
Monozygous (identical) twins	-	1	-
Parent-child	1st degree	1/2	1/4
Brother-sister (including fraternal twins)	1st degree	1/2	1/4
Brother-half sister	2nd degree	1/4	1/8
Uncle and aunt-nephew and niece	2nd degree	1/4	1/8
Half uncle-niece	3rd degree	1/8	1/16
First cousins	3rd degree	1/8	1/16
Double first cousins	2nd degree	1/4	1.8
Half-first cousin	4th degree	1/16	1/32
Second cousin with uncle and aunt	4th degree	1/16	1/32
Second cousins	5th degree	1/32	1/64

Table 2: Frequency of aminoacidopathies

Disorder	*n*	Percentage	
		Aminoacidopathies	Total metabolic disorders
Tyrosinemia	28	50.9	7.1
MSUD	18	32.7	4.6
Homocystinuria	7	12.7	1.8
Lysinuric protein intolerance	1	1.8	0.25
Nonketotic hyperglycinemia	1	1.8	0.25
Total	55	100	14

MSUD: Maple syrup urine disease

Aminoacidopathies were slightly more prevalent in girls than boys (56.9% vs. 43.1%) with 89.2% of the patients coming from consanguineous marriages. 76.6% of patients required hospitalization and tyrosinemic patients had the highest frequency of hospitalization (over 10 times). Of the patients with aminoacidopathies, 49% presented during neonatal period and 39% at 1–12 months of age. The onset of presentation in tyrosinemic patients was more frequent (50%) in the age group of 1–12 months. Maple syrup urine disease (MSUD) had the highest frequency of symptom presentation (61%) in neonatal period, and most (44.4%) of the MSUD patients were diagnosed at this time. However, the highest number of patients with aminoacidopathies (47.7%) was diagnosed in the age group of 1–12 months. The most prevalent symptoms in this group of patients were developmental disorders and convulsions while half presented with growth disorders at follow-up [Table 3].

Nearly, 12.5% of patients studied in regular schools and the rest attended special schools or were not trainable. Previous infant death in the family was reported in 8.9% of patients. The prevalence of abortion was 19.6% mainly due to homocystinuria (28.6%). Mortality rate was reported in 35.5% of patients. One-third of deaths was reported in the MSUD subgroup.

Discussion

The findings of this research revealed that 89.2% of patients suffering from aminoacidopathies were from consanguineous marriages, 73% of which took place between first cousins. This finding represents the high rate of consanguineous marriage in the region of study, as with other Middle East countries such as Lebanon and Saudi Arabia.[5,12] Our data indicated that organic acidemia was three times more frequent than aminoacidopathies, which is inconsistent with the studies conducted in other countries including Oman, Lebanon, and Saudi Arabia where aminoacidopathies have been reported to be 3 times more frequent than organic academia.[13,14] The higher frequency of phenylketonuria and tyrosinemia is in agreement with the studies in other Middle Eastern countries and Mediterranean region such as Italy and Tunisia.[11,15,16] Table 4 compares the frequency of aminoacidopathies in our study and other studies. In the study by Pishva *et al*. in Shiraz, South of Iran, MSUD was reported to be less frequent than our study (7.4%).[17] In this study, approximately half of the patients had delayed diagnosed after 1 year of age because of the unavailability of newborns screening. This is despite the fact that 88% of the presentations mostly occur in the 1st year, and the diagnosis was mainly based on clinical symptoms.

Male to female ratio was 1.3/1 in our study which is inconsistent with the studies in Libya and Lebanon (1/1.2).[18,19] This inconsistency in the findings could not be clearly explained. The diagnosis of tyrosinemia and MSUD was mainly made before the 1st year of life, but other disorders were diagnosed at 1–5 years of age. The onset of clinical symptoms of MSUD, tyrosinemia, and nonketotic hyperglycinemia was seen mainly in neonates. According to the study by Laila in Egypt, the diagnosis of homocysteinuria and tyrosinemia was made after the 1st year of life, but MSUD and nonketotic hyperglycinemia were identified prior to 3 months of age.[20] The Libyan study

Table 3: Frequency of clinical symptoms in aminoacidopathy patients

Subtype of aminoacidopathy	Liver disorders (%)	Seizure (%)	Developmental delay (%)	Growth retardation (%)	Hypoglycemia (%)	Acidosis (%)	Hyperammonia (%)	Eye disorders (%)	Renal disorders (%)
Tyrosinemia	46.40	17.90	17.90	53.50	10.70	3.60	0	0	3.50
MSUD	5.50	38.90	44.40	61.10	11.10	16.70	0	0	0
Homocystinuria	0	28.50	71.40	42.80	0	0	0	42.80	0
Lysinuric protein intolerance	0	100	100	0	0	0	100	0	0
Nonketoetic hyperglycinemia	0	100	100	100	0	0	0	0	0
Total	18.60	23.70	30.50	49.10	8.40	8.40	1.60	6.70	5

Table 4: Relative frequency of aminoacidopathies compared to previous studies

Study	Present study	Tunisia 15	Italy 11	Lebanon 19	Saudi Arabia 14	Oman 13
Total patient in study	392[a]	370[a]	404[a]	294	98	25
Patient with aminoacidopathy	59	212	161	211	50	16
Percent patient with aminoacidopathy	15	57	161	72	51	64
Common aminoacidopathy	PKU/tyrosinemia	PKU/MSUD/tyrosinemia	PKU/MSUD/HCY	PKU/MSUD	PKU/MSUD	UCD

[a]Without PKU. PKU: Phenylketonuria, MSUD: Maple syrup urine disease, HCY: Homocystinuria, UCD: Urea cycle disorder

showed that all disorders were diagnosed before 1 year of age, except homocysteinuria which was diagnosed at the age of five. According to research conducted in Lebanon, tyrosinemia, and nonketotic hyperglycinemia were diagnosed at ages prior to 1 year and MSUD was diagnosed at a wide range of ages from 7 days to 13 years. Overall, one-third of patients was diagnosed prior to 1 year of age.[19] The interval between the onset of disease and delay in diagnosis highlights the importance of newborns screening programs. Although no clinical suspicion among the physicians and referring system and a variety of the symptoms of these disorders could contribute to the late diagnosis.

The prevalence of aminoacidopathies varies worldwide. In this study, the overall prevalence of aminoacidopathies was 9/100,000 (1/10,989). In England, the incidence proportion of aminoacidopathies, irrespective of phenylketonuria, was 1/5354, in Canada 1/6606, in Libya 1/6158, and in Italy 1/36,389.[21] The frequency of aminoacidopathies in our study was lower than that in Germany (33.3%), The Netherlands (33.7%), Austria (41%), France (34.6%), Brazil (19.3%), Egypt (62.6%), Libya (25%), and Tunisia (57.3%) and approximately similar to that in Denmark (15.4%) and Saudi Arabia (16%).[14,18,20,22]

Tyrosinemia was the most common subgroup in this study, seen in 1/21,509 live births which are consistent with rates in Qatar.[18] However, the study by Laila in Egypt, Lebanon, and Tunisia reported a higher prevalence of MSUD.[18-20] Pishva *et al*. (Shiraz, Iran), calculated a similar frequency of aminoacidopathies compared with the present study (including patients with phenylketonuria) but MSUD was reported as the most prevalent subgroup of aminoacidopathies (46.6%).[17]

Clinical suspicion plays a vital role in detection of aminoacidopathies. In developed countries, newborn babies are screened for multiple metabolic diseases. In other countries, a more limited form of screening is performed.[17] The prevalence rates reported in the present study are likely to be much lower than the actual rates, which may be due to selective screening and failure to refer these patients to endocrine centers.

Family history greatly assists in the diagnosis of these disorders. Consanguineous marriage not only predisposes the offspring to acquire inherited disorders but causes an increase in the frequency and pathogenicity of genes in subsequent generations, thus, increasing the risk of acquiring autosomal recessive diseases.[10] In our study, consanguineous marriages were highly frequent. In Turkey, Stike reported consanguineous marriage as a main reason for metabolic disorders in this country.[23] The study by Hamadwaleed in Saudi Arabia showed that consanguineous marriage was a risk factor for metabolic disorders which lead to a 60% predisposition to the development of genetic diseases.[24] In this study, consanguineous marriage was more frequent between the parents of children with aminoacidopathies than the study in Lebanon (60%), but family history of metabolic disorders was higher in Lebanon (21%).[19] The reported frequency of consanguineous marriage by Nithiwat in Thailand was much lower than our study (56%).[25]

The symptoms and presentations of disorders depend on the type of study and the prevalence of disorder in the studied region. In the symptomatic patients of our study, neurological manifestation was the main presentation of inherited metabolic disorders (54.2%). Reduced IQ, delayed psychomotor development, and convulsion could alarm the physician toward the presence of metabolic diseases. MS/MS tests can be performed to confirm the suspected diagnosis. Liver diseases such as acute or chronic liver failure and coagulation disorders were seen in most patients with tyrosinemia (46.4%). Growth retardation was seen in half of the patients with aminoacidopathies. The clinical symptoms in the patients with tyrosinemia, homocysteinuria, nonketotic hyperglycinemia and MSUD in our study were consistent with other studies.[17,18,20,24] However, the symptoms in MSUD patients in our study were different from Pishva in Shiraz who presented with Lethargy, poor feeding, and convulsion.[17]

In this study, the mortality rate in aminoacidopathic patients was 30%, most of whom were suffering from MSUD. The rate of death and mental retardation due to aminoacidopathies has been reported as 67% in Nithiwat, Thailand with the highest mortality in nonketotic hyperglycinemia.[25] Research conducted in Libya showed that all the patients died but in this study over 60% of the MSUD patients survived.[18] Unfortunately, socioeconomical factors prevent a large proportion of the patients from accessing specialized formulas who were instead breastfed or fed with the wrong formulas which load to delayed development, neurologic deficits, and increased mortality rates.

Limitations of the study

Limitations of this study include failure to include some patients because they could not pay for laboratory test or were lost to follow-up.

Conclusion

Although metabolic disorders are identified as rare diseases, they are more prevalent in the studied population of

Isfahan. These disorders place a large financial burden on the families and communities. Prenatal diagnosis, which is not yet available, and genetic counseling in families with history of such disorders can be effective steps in addressing this illness, particularly in the communities with high rates of consanguineous marriages. Further studies are needed to investigate the utility and economic value of screening various programs, particularly for tyrosinemia, which has a relatively higher frequency. This can lead to earlier initiation of rehabilitation, special diets/formulas, and special care which can minimize repeated hospital admissions and reduce the burden of disease on patients.

Acknowledgment

Hereby, we gratefully thank Mrs. Zarnam for appropriately gathering data, the patients' families for their satisfactory collaboration during the study, Department of Census and Statistics for assisting us in gathering the data of births, and Deputy of Research of Isfahan University of Medical Sciences.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Champion MP. An approach to the diagnosis of inherited metabolic disease. Arch Dis Child Educ Pract Ed 2010;95:40-6.
2. Huang X, Yang L, Tong F, Yang R, Zhao Z. Screening for inborn errors of metabolism in high-risk children: A 3-year pilot study in Zhejiang Province, China. BMC Pediatr 2012;12:18.
3. Waisbren SE. Expanded newborn screening: Information and resources for the family physician. Am Fam Physician 2008;77:987-94.
4. Scriver CR, Beaudet A, Sly WS, Valle D. The Metabolic and Molecular Bases of Inherited Metabolic Diseases. 8th ed. New York: McGraw-Hill; 2001.
5. Tadmouri GO, Nair P, Obeid T, Al Ali MT, Al Khaja N, Hamamy HA. Consanguinity and reproductive health among Arabs. Reprod Health 2009;6:17.
6. Burlina AB, Bonafé L, Zacchello F. Clinical and biochemical approach to the neonate with a suspected inborn error of amino acid and organic acid metabolism. Semin Perinatol 1999;23:162-73.
7. Wilcken B, Wiley V, Hammond J, Carpenter K. Screening newborns for inborn errors of metabolism by tandem mass spectrometry. N Engl J Med 2003;348:2304-12.
8. Ellaway CJ, Wilcken B, Christodoulou J. Clinical approach to inborn errors of metabolism presenting in the newborn period. J Paediatr Child Health 2002;38:511-7.
9. Golbahar J, Al-Jishi EA, Altayab DD, Carreon E, Bakhiet M, Alkhayyat H. Selective newborn screening of inborn errors of amino acids, organic acids and fatty acids metabolism in the Kingdom of Bahrain. Mol Genet Metab 2013;110:98-101.
10. Shahri P, Namadmalan M, Rafiee A, Haghighizadeh MH. A case–control study of prevalence of consanguineous marriage among parents of handicapped and healthy children in Ahvaz. Jundishapur Scientific Medical J 2010:9:473-82.
11. Dionisi-Vici C, Rizzo C, Burlina AB, Caruso U, Sabetta G. Inborn errors of metabolism in the Italian pediatric population: A national retrospective survey. J Pediatr 2002:140:321-9.
12. Al-Gazali L, Hamamy H, Al-Arrayad S. Genetic disorders in the Arab world. BMJ 2006;333:831-4.
13. Joshi SN, Hashim J, Venugopalan P. Pattern of inborn errors of metabolism in an Omani population of the Arabian Peninsula. Ann Trop Paediatr 2002;22:93-6.
14. Moammar H, Cheriyan G, Mathew R, Al-Sannaa N. Incidence and patterns of inborn errors of metabolism in the Eastern Province of Saudi Arabia, 1983-2008. Ann Saudi Med 2010;30:271-7.
15. Hadj-Taieb S, Nasrallah F, Hammami MB, Elasmi M, Sanhaji H, Moncef F, *et al*. Aminoacidopathies and organic acidurias in Tunisia: A retrospective survey over 23 years. Tunis Med 2012;90:258-61.
16. Khemir S, El Asmi M, Sanhaji H, Feki M, Jemaa R, Tebib N, *et al*. Phenylketonuria is still a major cause of mental retardation in Tunisia despite the possibility of treatment. Clin Neurol Neurosurg 2011;113:727-30.
17. Pishva N, Mirzaee A, Karamizade Z, Pourarian S, Hemmati F, Razvi M, *et al*. Selective screening of high-risk Iranian patients for the detection of inborn error of metabolism. Iran J Neonatol 2014;5:11-14.
18. AlObaidy H. Patterns of inborn errors of metabolism: A 12 year single-center hospital-based study in Libya. Qatar Med J 2013;2013:57-65.
19. Karam PE, Habbal MZ, Mikati MA, Zaatari GE, Cortas NK, Daher RT. Diagnostic challenges of aminoacidopathies and organic acidemias in a developing country: A twelve-year experience. Clin Biochem 2013;46:1787-92.
20. Selim LA, Hassan SA, Salem F, Orabi A, Hassan FA, El-Mougy F, *et al*. Selective screening for inborn errors of metabolism by tandem mass spectrometry in Egyptian children: A 5 year report. Clin Biochem 2014;47:823-8.
21. Sanderson S, Green A, Preece MA, Burton H. The incidence of inherited metabolic disorders in the West Midlands, UK. Arch Dis Child 2006;91:896-9.
22. Wajner M, Coelho Dde M, Ingrassia R, de Oliveira AB, Busanello EN, Raymond K, *et al*. Selective screening for organic acidemias by urine organic acid GC-MS analysis in Brazil: Fifteen-year experience. Clin Chim Acta 2009;400:77-81.
23. Aygen S, Dürr U, Hegele P, Kunig J, Spraul M, Schäfer H, *et al*. NMR-based screening for inborn errors of metabolism: Initial results from a study on Turkish neonates. JIMD Rep 2014;16:101-11.
24. Al Bu Ali WH, Balaha MH, Al Moghannum MS, Hashim I. Risk factors and birth prevalence of birth defects and inborn errors of metabolism in Al Ahsa, Saudi Arabia. Pan Afr Med J 2011;8:14.
25. Vatanavicharn N, Ratanarak P, Liammongkolkul S, Sathienkijkanchai A, Wasant P. Amino acid disorders detected by quantitative amino acid HPLC analysis in Thailand: An eight-year experience. Clin Chim Acta 2012;413:1141-4.