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Original Article

Selective Screening of High-risk Iranian Patients for the Detection of Inborn Error of Metabolism

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ABSTRACT

Background: Despite the rarity of metabolic diseases (the overall incidence of 1:2000 cases), these conditions can lead to devastating and irreversible effects if not diagnosed and treated promptly. Selective screening is considered an acceptable method for the detection of these diseases with multiple presentations.

Methods: Panel neonatal screening was applied for the detection of metabolic diseases in 650 high-risk Iranian patients in Fars province, Iran. The inclusion criteria were lethargy, poor feeding, persistent vomiting, cholestasis, intractable seizures, decreased level of consciousness, persistent hypoglycemia, unexplained acid-base disturbance, and unexplained neonatal death.

Results: Organic acidemia with 40 cases (42%) was the most frequent disorder diagnosed in our high risk populations, followed by disorder of galactose metabolism (30%), 15 patient had classic galactosemia (GALT<5%). Methyl Malonic acidemia and propionic acidemia were the most common, they become symptomatic from three days to several months after birth. The most common symptoms in these patients were repeated vomiting, respiratory distress and lethargy. Most patient had repeated hospitalization even on special formula. Disorder of amino acid metabolism also is not uncommon (17%) in this high risk population, MSUD was the most common.

Conclusion: Metabolic diseases are not rare in Iranian populations. Consequently, sensitive methods for prompt diagnosis and treatment are required in our country.

Keywords: Fars, Metabolic disorders, Screening

Introduction

Inborn error of metabolism (IME) with an overall incidence of 1/2000 population represent a common cause of diseases in newborn period. Most infant with IEM are normal at birth, and the signs often develop in hours to days after birth (1,3).

IEM are part of the differential diagnosis of many infants admitted in PICU (2). Most of them are transmitted as autosomal ressesive genetic traits. A history of parental consanguinity, unexplained neonatal death or sever illness in family should alert the clinician to the possibility of an IEM (3).

Acute symptoms that are particularly associated with IEM include encephalopathy, intractable seizures, hepatic failure, cardiomyopathy, metabolic acidosis and hypoglycemia (2).

Many IEM are amenable to treatment with early diagnoses, for others that are not amenable to treatment, establishing the diagnosis in the index case is important for prenatal diagnosis in subsequent pregnancy. Therefore, selective screening for inherited metabolic disease represents a major challenge to modern preventive medicine (3). Today the development of new modalities for diagnosis of these disease offers the potential substantially changing the natural history of these disease by reducing the mortality and morbidity. We used the panel newborn screening for diagnosis of aminoacidemias, organic acidemiase, fattyacid oxidation defect and galactosemia .Our purpose was to establish the prevalence of IEM in high risk population, as well as to raise the awareness of these disorders as an important group of genetic disease for medical community.

Material and methods

Over a period of four years (2007-2011) 650 patients with clinical features of IEM were admitted at the hospitals affiliated to Shiraz University of Medical sciences, these children were from Fars province and other provinces in south of Iran.

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Table 1. Inborn error of metabolism detected in the populations from south of Iran

Diseases	Number of patients (%)
Number of patient analyzed	650
Number of patient diagnosed	94(14%)
Galactosemia	27(29%)
MMA, PPA, Cobalamin deficiency	22(23.5%)
Isovaleric academia	7(7.6%)
Glutaric academia type I	8(8.5%)
MSUD	7(7.4%)
Phenylketonuria	4(4.2%)
Citrulinemia	3(3.2%)
Other	15(16%)

The following clinical features were used as inclusion criteria for investigation of the patients.

Lethargy, poor feeding, persistent vomiting, cholestasis, intractable seizure, decreased level of consciousness, persistent hypoglycemia, unexplained acid base disturbance and unexplained neonatal death.

Sample collection

Blood samples were collected on filter paper and dried for 3-4 hours at room temperature and shipped frozen with dry ice to Wagner laboratory in Germany and lab test was done by neonatal screening panel.

Result

From the 650 symptomatic children screened over a period of 4 years 92 were diagnosed as IEM. The mean age was 15 months, from 15 days to 6 years. Sixty four were male and twenty eight were female (Table 1).

Disorder of metabolism of galactose

Of 27 patient with high galactose 15 had classical galactosemia (GALT<5%), 4 patients had high galactose and galactose -1-posphate, 9 patients had high galactose (one was diagnosed as Fanconi–Bickel syndrome). The most clinical finding were prolonged hyperbilirubinemia, followed by lethargy, poor feeding and liver failure.

Table 2. Clinical finding in patients with IEM

IEM	Clinical feature
PPA OR MMA	Lethargy, poor feeding, vomiting, coma, respiratory distress, metabolic acidosis, death
galactosemia	Hyperbili, poor feeding, lethargy, hepatic failure
Isovaleric acidemia	Poor feeding, lethargy, coma
Glutaric acidemia type I	Macrocephaly developmental regression, dystonia
MSUD	Lethargy, poor feeding, convulsion, coma, metabolic acidosis
Phenylketonuria	Seizures, microcephaly, light colored skin and hair
Citrullinemia	Poor feeding, lethargy, vomiting, coma
Carnitin Transcarbomilase deficiency	Hepatic disease, cardiomyopathy, coma

Disorder of organic acid metabolism

Methyl malonic acidemia or propionic acidemia were the most common organic acidemia followed by Glutaric -acidemia type I and the isovaleric acidemia other organic acid disorders were relatively rare .patients with MMA or PPA were presented with lethargy, poor feeding, metabolic acidosis pancytopenia, coma and respiratory arrest.

Amino acid disorders

Among the disorders of amino acid metabolism, Maple syrup urine disease was the most common

Table 3. Abnormal parameter of disorder of amino acid metabolism

Aminoacidemias (n=15)		Abnormal parameter	Concentration mean range(µmol/L)	Reference range
Phenylketonuria	4	Phenylalanin	1113(412-1951)	151
		Phenylalanin/Tyrosine ratio	18(11-39)	2.5
Citrllinemia	2	citrullin	1031(457-1606)	<60
Tyrosinemia type I	1	Tyrosine	832	<72
		succinylacetone	Markedly elevated	
Hmocystinuria	1	Methionin	High	
MSUD	7	Leucie+Isoleucine	2646(490-4278)	<350
		The ratio (Leucine-Isolucine)/Phe	76(13-111)	<10
		Valine	266(97-684)	<250

Table 4. Level of abnormal parameters for different organic acidemias

Organic acidemias	n	Abnormal parameter	Concentration	Reference range (µmol/L)
MMA or PPA	22	Propionylcarnitin	14(3.84-57)	2.5
		Propionylcarnitin/acetylcarnitin	0.58(0.17-2.5)	<0.13
Lsovaleric acidemia	7	Isovaleryl carnitin	(14.2-8.5)	0.16
		Isovaleryl carnitin/acetylcarnitin	0.32(0.03-0.75)	<0.01
Glutartic academia type I	8	Glutaryl carnitin	1.1(0.84-1.50)	<0.06
Biotidinase deficiency	2	3-hydroy isovaleryl carnitin	2.5(1.8-3.2)	0.5
Multiple carboxylase deficiency	1	3-hydroxy isovaleryl carnitin	1.2	0.5
		Propionyl carnitin	16.64	2.5

Table 5. Abnormal parameter of galactose metabolism

High galactose	27
Low GALT	15
High Galactose-1-phosphate	19
other	Fanconi Bickel

followed by phenylketonuria and Citrullinemia. Tyrosinemia type I and homocystinuria were relatively rare. In MSUD the characteristic finding were lethargy poor feeding, convulsion, coma, spasticity and metabolic acidosis. All of the patients had brain edema in CT scan.

Fatty acid oxidation defect

625 patients investigated, four children had fatty acid oxidation disorder. Two with carnitin transcarbamilase deficiency, one had Medium-Chain-A CO-dehydrogenase deficiency and one had mitochondrial fatty acid oxidation defect.

The clinical findings and abnormal parameters that detected are shown in Table 2-5.

Discussion

Although early diagnosis of metabolic diseases is very effective in the treatment of these disorders, neonate are screened for few diseases even in the developed world so selective screening is important for diagnosis of specific IEM.

Specific protocol for selective screening of IEM in high risk patient has been introduced since 1950 in several country. A constant improvement of analytical equipment and techniques for assaying has allowed the diagnosis an increasing number of disorder. We used the panel newborn screening for diagnosis.

A total of 92 (14%) of 520 symptomatic patients abnormal result were found in of our patients, which was lower than detection in Egyptian study, they diagnosed IEM in 22.73% of their patients (6), in another study in Karachi the detection rate was 16 out of 62 (25.8%)(9). However several other studies, two in Brazillian (7,8) and one Indian (4) reported lower detection rate 6.5%, 3.17% and 3.2% respectively .Different detection rate in different studies can be due to different criteria for selection of high risk patients and availability of local facility for diagnosis of IEM.

Of these 22 patient had high propionyl carnitin (methy malonic acidemia. Propionic acidemia and cobalamin deficiency), 27 had disorder of galactose metabolism, 8 had Glutaric acidemia typ 1, 7 had MSUD,7 had Isovaleric acidemia, 4 had phenylketonuria, 3 had citrullinemia, 2 had Argininosuccynyl acidemia, 2 had biotidinase deficiency, 1 had multiple carboxylase deficiency, 2 had carnitin transcarbomilase deficiency, 1 had either MC-ACO-dehydrogenase deficiency, Tyrosinmia type 1, Mitochondrial fatty acid oxidation defect, Aryelsulfatase deficiency, Canavan disease, GM2 gangliosidosis, Homocystinuria and Hexo Aminidase deficiency.

Organic acidemias with 40 cases (42%) was the most frequent disorder diagnosed in our high risk populations, followed by disorder of galactose metabolism (30%), 15 patient had classic galactosemia (GALT<5%).

Methyl Malonic acidemia and propionic acidemia were the most common, they become symptomatic from three days to several months after birth. The most common symptoms in these patients were repeated vomiting, respiratory distress and lethargy. Most patient had repeated hospitalization even on special formula. Disorder of amino acid metabolism also is not uncommon (17%) in this high risk population, MSUD was the most common.

MSUD was fairly common in other reports from Asian populations (10,11). MSUD patients become symptomatic at 3-7 days after birth, neurological symptoms were the most common (lethargy, poorfeeding, convulsion, dystonia and coma).

CT scan showed generalized brain edema in all of our patients. Death occurred in 4 out of 7 patients and the other three patients showed mental and motor developmental delays on special amino acid formula and low protein diet. Msud had the poorest outcome among the aminoacidemias.

Of 15 patients with classical galactosemia (GALT activity below 5%) all except one presented with cholestasis. The most common symptoms were jaundice, lethargy and poor feeding. Cataract was also common in our patients (41%).

In a selective study in Karachi organic acidemias were also the most common and represented 62% of their patients (6). In another study in India PKU was the most common disorder (4). PKU is not rare in this country, in study by J. Golbahar et al the incidence of PKU was 27/100000 population (5), lower rate of PKU in this study is due to early detection by screening test. Screening test also take place for galactosemia but in another our study 100% of patient with galactosemia were symptomatic before screening results.

In a selected screening of 231 cases in Egypt organic acidemia was the most common (6), in

another study in Brazilian patients, PKU and GM1 gangliosidosis were the diseases with the highest incidence (7).

Fatty acid oxidation defect was relatively rare in this study this is comparable with other study by Moacir Wajner et al (8) and another study in India (4).

We need more sensitive method like MS/MS for separation of organic acidemias.

Fortunately one local facility with this modality already has started its work in this town.

Conclusion

Although metabolic diseases individually are rare but overall are a common causes of neonatal disease, early diagnosis and treatment can prevent death in many of them but cure doesn`t occur, they survive with mental and motor developmental delay, they need rehabilitation, repeated hospitalization, special formula and associated cost might represent a heavy burden for families with low and middle social economic incomes. Detection of specific mutation is necessary for familial counseling in this country with high rate of consanguineous marriage (12). The government should increasing insurance coverage to patients with IEM.

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