Original Article

The Prevalence of Phenylketonuria and other metabolic diseases in sick Iraqi children; the importance of the newborn screening program.

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Summary:

Background: Phenylketonuria (PKU) is one of the most important metabolic cause for mental retardation in children, in which early diagnosis would successfully prevent mental retardation, yet, there are some other serious metabolic diseases that share the same mode of presentation and some of the phenotypic manifestations also.

Aim: This study aimed to assess the prevalence of PKU and other inborn errors of metabolism among sick children, presenting with clinical features suggestive of PKU, what are the diseases that share same clinical presentation of PKU, and make a proper early diagnosis and management when possible.

Methods: During the period from August 2009 to August 2011, 63 cases were referred to the Children Welfare Teaching Hospital (CWTH) with clinical features of PKU, all were enrolled in this study, few blood drops on a special filter paper were taken from each patient and sent to a specialized metabolic laboratory in Saint Joseph University \Beirut, using tandem mass spectrophotometry (MS/MS). The results were received through internet after being analyzed and interpreted.

Results: out of the 63 cases, only 28(44.4%) came positive with different diseases, only 7(11.1%) were cases of PKU. The results also showed some other Inborn Errors of Metaboilsm(IEM): homocystinuria(HCY)or methionine adenosyltransferase(MAT) 7(11.1%),Methylmalonic academia (MMA)4(6.3%), maple serum urine disease (MSUD) in 3 cases(4.7%).The consanguinity was positive in 41 cases (65%). Positive family history was documented in 23(36.5%).All PKU cases had the background of consanguineous marriages (100%).

Conclusions: PKU is one of the most important metabolic cause for mental retardation in our study, but some other serious metabolic defects like homocystinuria(HCY) or MAT, organic acidemias, maple syrup urine disease(MSUD) also cause mental retardation and share some of the phenotypic manifestations of PKU. Many families had positive history of affected siblings,especially those with consanguineous marriages.

Keywords: Phenylketonuria , PKU , mental retardation, metabolic diseases, inborn errors of metabolism , tandem mass spectrophotometry (MS/MS).

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Introduction:

Phenylketonuria (PKU) was discovered by the Norwegian physician IvarAsbjørnFølling in 1934(1). It is a genetic disorder due to inability of the body to utilize the essential amino acid, phenylalanine (2,3). In 'classic PKU', the enzyme that breaks down phenylalanine hydroxylase, is deficient, phenylalanine accumulate in the blood and body tissues, causing significant brain damage. The incidence of Classic PKU is one in every 10,000 to 20,000 Caucasian or Oriental births (4), which increase with consanguineous Marriages (2,5). In Iraq, the total consanguinity rate is around 50%, and degree of first cousin marriages is about 30% (6). Infants with PKU appear normal at birth, many have blue eyes and fair hair and skin, vomiting, irritability, an eczema-like rash, and a mousy odor to the urine, active muscle tendon reflexes(2). Later, mental retardation and seizures, microcephaly occurs. Phenylalanine free diet should be started as soon as diagnosis is established.

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Other similar diseases includes, homocystinria(HCY) or methionineadenosyltransferase (MAT) deficiency.

Homocystinuria is an autosomal recessive IEM usually caused by a deficiency of Cystathionine beta-synthatase and associated with elevations of homocysteine in plasma and urine (7). Clinical features include a tall, slender habitus, scoliosis, arachnodactyly, muscle weakness, genu varus, thin blond hair(8), malar flush, lens dislocations, and mental retardation(8). Treatment with a trial of oral vitamin B6 supplementation, folic acid, Vitamin B12 may also be helpful(9). HCY was most of times compared to MAT,as they both have high levels of plasma methionine levels and similarities in presentation(6,10). Methionine adenosyltransferase deficiency is an IEM resulting in isolated hypermethioninemia(6,10). MAT was first described in 1974(11,12), complete absence of MAT activity may result in neurologic signs and symptoms Methylmalonic acidemia (MMA),in which newborns presenting with progressive encephalopathy(13), and secondary hyperammonemia, poor growth, seizures ,microcephaly, mental retardation, and skin rashes(8). Maple syrup urine disease (MSUD) is an autosomal

recessive metabolic disorder. The condition gets its name from the distinctive sweet odor of maple of the urine (14). It presents with lethargy, hypotonia , seizures, hypoglycemia, opsotonus, coma and neurological decline (15).This study aimed to assess the prevalence of PKU and other inborn errors of metabolism among sick children referred to children welfare teaching hospital, presenting with clinical features suggestive of PKU, what are the diseases that share same clinical presentation of PKU, and make a proper early diagnosis and management when possible.

Patients and methods:

over a period of two years, from the first of August 2009 till the first of August 2011, 63 children referred to the children welfare teaching hospital(CWTH) as highly suspected cases of PKU, were enrolled in this study. With the collaboration of the Saint Joseph university\Beirut, and the Children Welfare Teaching Hospital (CWTH),blood samples in the form of few blood drops were taken on specially designed filter papers, sent through the DHL to Beirut. Those samples were analyzed for metabolic diseases , using the tandem mass spectrophotometery (MS\MS) technology .Results of the tests analysis were interpreted by specialized metabolic team ,reports were sent back through the internet. In this study,we included sick children with signs and symptoms raising suspicion of PKU (e.g. mental retardation, intellectual deficiency,repeated fits, microcephaly, fair hair and skin, abnormal odors of urine). Children with other signs and symptoms suggesting IEM (e.g. jaundice, organomegaly , hypoglycemia ..)were excluded from this study, taking in consideration that patients with PKU do not usually present with these symptoms. Cases were referred from different specialties,mostly from the GIT department, neurological department, and private doctor's clinics). Results were expressed in numbers and percentages. Statistical analysis: patients data were tabulated and processed using Microsoft office 2010 (excel work sheet) ,qualitative data are expressed as frequency and percentage quantitative data as mean and SD (standard deviation).

Results:

The total number of sent samples was 63, out of which 32(50.7%) were females,31 (49.3%) were males, 26(41.2%) were below one year of age,33(52.3%) were from 1-5 years of age,and 4(6.3%) above 5 years of age. Twenty eight cases (44.5%) were positive with different diseases, but only 7(11.1%) were cases of PKU. Homocystinuria or methionine adenosyltransferase dificency(HCY or MAT) were 7(11.1)% cases ,methylmalonic academia MMA were 4(6.3%) cases, (maple serum urine disease)MSUD 3(4.7%) cases,(short chain acyleco.A carboxylase deficiency) SCAD 2(3.17%), biotidinase deficiency 2(3.17%) cases, high alanine with suspected mitochondrial disease2(3.17%), low carnitine profile 1(1.58%). The consanguinity was positive in 41 cases (65%), negative in 15 cases (23.8%), and unknown in 7(11.1%). Positive family history of affected siblings was documented in 23 / 63 cases(36.5%), negative in 13(20.6%), unknown in 27(42.8%).

Table 1: Results of tandem mass spectrophotometery of the 63 positive cases

Phenylketonuria (PKU)	7	(11.11%)
Homocystinuria or methionineadenosyl transferase deficiency (HCY or MAT)	7	(11.11%)
Methylmalonicacidemia (MMA)	4	(6.3%)
Maple syrup urine disease(MSUD)	3	(4.7%)
Short chain AcyleCo.A carboxylase deficiency(SCAD).	2	(3.17%)
Biotinidase deficiency.	2	(3.17%)
High alanine with suspected mitochondrial disease.	2	(3.17%)
Low carnitine profile	1	(1.58%)
Total	28	(44.4%)

The most common presenting symptoms were mental retardation and intellectual delay in 58 / 63 (92%), spasticity 17(26.9%), repeated seizures 14(22.2%), blonde complexion 11(17.4%), microcephaly 9(14.2%), hypotonia 3(14.6%),eye abnormalities 2(3.1%), thromboembolic phenomenon 1(1.5%).

Table 2: The clinical presentation of 63 cases

Total NO. of patients	63	100%
Mental retardation and intellectual delay	58	92%
Spasticity	17	26.9%
Repeated seizures	14	22.2%
Blonde complexion	11	17.4%
Microcephaly	9	14.2%
Hypotonia	3	4.7%
Ophthalmological problems(e.g. blindness, nystagmus)	2	3.1%
Abnormal body odor	2	3.1%
Thrombo embolic phenomenon	1	1.58
Positive consanguinity Negative consanguinity Unknown	41 15 7	65% 23.8% 11%
History of affected siblings	23	36.5%

Note: there is an overlap in clinical signs and symptoms.

Table 3: The characteristics of seven PKU cases

Total NO. of PKU patients	7	100%
Gender: Females	4	57%
Males	3	43%
Mental retardation	6	85.7%
microcephaly	4	57%
Blonde complexion	4	57%
Repeated seizures	2	28.5%
Abnormal odor	0	0%
Consanguinity		
Positive	7	100%
Negative	0	0%
History of affected siblings:		
Positive	4	57%
Negative	3	43%

Note: there is an overlap in clinical signs and symptoms.

Table 4:The characteristics of the 28 positive cases

Total NO. of positive cases	PKU	HCY or MAT	MMA	MSUD	Other diseases
28 (100%)	7(25%)	7(25%)	4(14.2%)	3(10.7%)	
Female:13(46%)	4(53%)	5(71%)	1(25%)	2(66%)	7(25%)
Male :15(44%)	3(47%)	2(29%)	3(75%)	1(33%)	
Mental retardation	6(21.4%)	6(21.4%)	4(14.2%)	3(10.7%)	
microcephaly	4(14.2%)	2(7.1%)	2(7.1%)	1(3.5%)	
Blonde complexion	4(14.2%)	2(7.1%)	2(7.1%)	1(3.5%)	
seizures	2(7.1%)	3(10.7%)	2(7.1%)	1(3.5%)	
Positive consanguinity	7(100%)	5(71.4%)	3(75%)	3(100%)	
Positive family history	4(57%)	3(43%)	2(50%)	3(100%)	

Discussion

It was found in this study that the number of patients PKU ,HCY and MAT are almost equal.

In table No.1, the number of cases of HCY or MAT is almost similar to PKU, next in order of results was the MMA and then MSUD. And their presenting features which were the marked mental retardation and intellectual delay in 92% of cases. While in Jailkhani R.et.al study(16) , the commonest clinical presentation was convulsions (30%). And in Vidya S. Patil et al. study(17), convulsions was also the most common presentation (25.7%),while in this study, the most common presenting feature was mental retardation(92%) while convulsions was only (22.2%) .In current study, history of sibling deaths was (36.5%), (15%)in Jailkhani R. et al (l6),while it was only (6.2%) in Vidya S. Patil et al(17) . The most common positive tests reported in this study were PKU, HCY or MAT, MMA and Branched Chain aminoaciduria(MSUD) while in Jailkhani R.(16) ,came across four interesting cases according to the frequency, they were, Phenylketonuria(PKU), Methyl malonicaciduria(MMA), Mucopolysaccharidosis and Branched Chain aminoaciduria (MSUD). While Vidya S. Patil et al(17) results showed ,nonspecific generalized aminoacidurias, branched chain aminoacidurias maple serum urine disease (MSUD) , methlymalonicaciduria and phenylketonuria.These diseases are the most common metabolic causes of mental retardation and seizures in children(2,5,7) .All these diseases are of autosomal recessive inheritance, consanguineous marriages are quite common in Iraq and other middle east countries (6) ,this explains the high rate of metabolic disorders in these families (65%).While the incidence of positive consanguinity in Vidya S. Patil et al was only(17%).The frequency PKU is dramatically decreasing among the countries since screening during the neonatal period can be performed for several conditions, it is critical and crucial to decide, in the light of available resources and epidemiological trends, which diseases should be screened for and what are the priorities for

countries of the region (18). Newborn screening tests through the tandem mass spectrophotometery are expanding among the world(18,19) ,after it has been established in the developed countries, many newborn screening challenges are facing the developing countries , Iraq is one of these countries. Most if not all of the screening programs would include PKU ,as one of the commonest inborn errors of metabolism(IEM) that stands behind tragic pediatric conditions such as mental retardation, epilepsy ,growth retardation ,what makes it very important is it's being treatable if picked and diagnosed early(2) .MS/MS technology can assist in diagnosing metabolic disorders during the newborn period that previously were diagnosed only after development of symptoms (when it is too late). Pre symptomatic detection now allows treatment initiation while the infant is healthy and assists in defining the spectrum of clinical disease related to these disorders (2). MS/MS technology can be used advantageously to screen for selected amino acid disorders for which other newborn screening methods are used. For example, MS/MS can accurately detect elevated phenylalanine levels in dried blood spots taken from infants as young as age ≤24 hours (20). By using the MS/MS-detected phenylalanine/ tyrosine ratios, physicians can diagnose PKU earlier and rely on an assay with a reduced false-positive rate .In this study ,and at this time when no newborn screening program had yet been launched in Iraq, most of the blood samples were taken from diseased children coming from different localities, presenting with different signs and symptoms matching those of PKU, referred as suspected cases of PKU ,but the actual number ended up to be only7(11%) cases of PKU, taking in consideration that most of those children were symptomatic ,this was behind the high figure result .other diseases specially the HCY or MAT came in the same incidence rate of PKU, followed by the MMA and MSUD ,which makes it worthwhile to think of these possibilities specially in mentally retarded children . All of the PKU cases were related to consanguineous marriages, While in Vidya S. Patil et al(17) only 17% of cases came from related families, because in this study a very good number of cases came from ethnic society affected by traditions among Iraqi tribes(6).

Conclusion

PKU is one of the most common causes of preventable mental retardation in children, which should be screened for, and because early and proper diagnosis is very crucial. Similarity in presentation is common with other forms of IEM, for this reason a right diagnosis is to be made early and properly. PKU high incidence comes from the frequently happening consanguineous marriages in Iraq. Therefore Screening programs, prenatal diagnosis and genetic counseling are the cornerstones of the prevention and treatment of IEM.

Screening of newborns of previously affected siblings is mandatory.

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