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Inborn Errors of Metabolism Status in Iraq:

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Abstract*: Background and Objectives:- Inborn errors of metabolism(IEM) are genetically inherited diseases ,though individually rare, together they constitute a significant percentage of children presenting with acute problems. Diagnosis and follow up of IEM is integrated in several developed countries basic health care packages. This service is still limited in many developing countries including Iraq.*
Aim: We aimed to create awareness in the medical sectors about the existence and magnitude of the problem of IEM, to take steps towards setting the proper requirements for diagnosis of metabolic disorders, including neonatal screening program .
Methods*:This is both a prospective-retrospective study that included 1758patients with clinical manifestations suggestive of IEM collected from two major hospitals in Baghdad ,the Child Welfare Teaching Hospital(CWTH) and Al-Emamain AL Kadhemyian teaching hospital , in the period between the first of September 2009 and the first of September 2012.Filter paper blood samples were sent by fast mailing to Newborn Screening Laboratory/Saint Joseph University, Beirut, Lebanon. Samples were processed using tandem mass spectrophotometry(MS/MS),results analyzed and interpreted and sent back through net.*
Results *:Among 1758 samples analyzed ,females were 721(41%). Children below one year of age constituted 987(56%) including 164(9.3%)neonates , those between one year to five years were 606(34%),and ages > five years were 165(9.3%).*
Two hundred twenty four cases were identified and confirmed tohave IEM (12.7%). Ages below one year of age constituted 148(66%), ages > one year up to 5 years were 62(27.5%) and those> 5 years of age were14 (6%).
The metabolic disorders diagnosed were ,amino acid disorders 86(4.9%) ,mitochondrial disorders (fatty acids oxidation disorders and organicacidemias)were36(2%), glucose 6phosphate dehydrogenase deficiency 66(3.75%) ,carbohydrate metabolism disorders were 31 cases(1.76%), and endocrine disorders (congenital hypothyroidism) were 5(0.2%).One hundred seventy four (9.8%) cases had positive consanguineous marriage between father and mother ,while 132(7.5%) cases had positive history of a similar condition in the family or history of sudden infant death.
Conclusions*:-Amino acids disorders, fatty acids oxidation disorders and G6PDD are the most common metabolic disorders in the studied sample. The positive consanguinity and positive family history played important role in evolution of the suspicion of IEM in the patients.*
Key Words*: Inborn errors of metabolism , tandem mass spectrophotometer, neonatal screening and consanguinity.*

I. Introduction

Inborn errors of metabolism (IEM) are a heterogeneous group of disorders caused by genetic mutations and enzyme deficiencies constitute a wide spectrum of diseases in mankind which may manifest at any time from early neonatal period to adolescence. Some of the metabolic disorders may even present at adulthood(1,2).Theintroduction of MS/MS into neonatal screening has enabled the screening of conditions that might otherwise have been missed, and thus believed to be extremely rare (3,4), and before irreversible clinical damage occurs (5,6).

Most inborn errors of metabolism (IEM) surveys have been largely highlighted in Western countries, with few studies in developing country contexts. As well Newborn screening is integrated in all health policies in developed countries since the 70's of the last century (7). Such service is still relatively retarded in developing countries. Dried blood spot is currently wide spread as sampling device to detect IEM by MS/MS for newborns as well for older children, being easy to ship , relatively rapid and cheap, especially when related health facilities do not exist or are limited in the area (8). International efforts are now under way to help developing countries gain the knowledge and skills to improve IEM diagnostic and follow up .Since 2004, Middle East Metabolic Group by Orphan-Europe organizes annual meeting for that issue. In 2006, the National Institute of Child Health and Development launched Strengthening Newborn Screening in the Middle East and North Africa meetings,arranged each two year (9). This interactive regional gathering triggered collaboration like that between the Newborn screening Laboratory at St. Joseph University of Beirut-Lebanon and two major

teaching hospitals in Baghdad, AlKademyah University Hospital ,and the Medical City/ Child Welfare teaching Hospital, established since October 2009.

Iraq is a Middle Eastern country of over 30 Million populations count who have lived through extremely difficult conditions for many years. Despite that consanguinity incidence in the Iraqi society is relatively elevated at 40-49% (10), implying high prevalence of IEM, no efforts have been done in diagnosis and management of these diseases, and limited data had been reported about them.

Of the limited available regional reports, Al-AttiyahSa'ad reported in his medical thesis 2002 forty three cases of galactosemia(12), diagnosed over the period 1997-2002, in a major teaching hospital in Baghdad, depending mainly on clinical suspicion and simple primary level investigations. Awqati et al stated in 2009 that in Iraq Under-five years' child mortality is one of the highest in the Middle East region, with Diarrhea was the leading cause of death among infants (13). The latter symptom is common among many metabolic diseases. Hemoglobinopathies status in Iraq had been highlighted in previous papers such as G6PD deficiency, heamophilia and thalasemia (14,15).

The Iraqi Ministry of Health strategy 2009 - 2011 has put the primary care as the central plank of health care provision to the population, with emphases on competence, leadership, guidelines, standards and effective referral systems (11).

This concludes to the lack of IEM data; in addition to the fact that diagnostic facilities are very limited. In this study trials are made to highlight IEM status in Iraq.

Patients AndMethods :From December 2009 to December 2012, cases were selected from Al-Emamain AL Kadhemyian & The children's welfare teaching hospitals, as being suspected to have IEM, patients came from Baghdad & others referred from other governorates. clinical manifestations suggestive of metabolic diseases or IEM were as following (16,17):Neurological manifestations such as recurrent seizures, mental retardation, developmental, Gastrointestinal manifestations such as recurrent vomiting, chronic diarrhea, failure to thrive, prolonged neonatal jaundice, hepatomegaly, and splenomegaly or, Cardiac ,manifestations such as cardiomyopathy , Dysmorphic features ,patients with abnormal odors, lethargy and metabolic acidosis, or family history of previous deaths in the family or affected siblings with metabolic diseases,emphasizing on parental consanguinity. Samples using Ahlstrom® 226 were shipped by rapid courier to the newborn screening laboratory in Beirut/ St Joseph University. Samples were analysed for aminoacids, fatty acids, G6PD and thyroid stimulating hormone. Results were reported immediately via email.

For positive results , cases clinical correlation was assessed with the patients' records, that included the patients' medical history, , full physical examination & basic laboratory tests and imaging.

Data Analysis: The data are collected, analyzed, tabulated and figured by using the Microsoft office excel 2007. The data are expressed in form of numbers and percentages.

II. Results

Among 1758 samples analyzed between September 2009 and September 2012,females were 721(41%) .The majority of cases were below one year of age 987(56%), including 164(9.3%) neonates (from birth to 30 days of age) , ages ranging from > one year to five years of age were 606(34%), and ages above five years of age were 165(9.3%) .

As shown in table(1),two hundred twenty four cases were confirmed positive for IEM (12.7%). Males were 133 (59.5%) . The highest rate of positivity was in the neonatal period (19.5%) of the suspected cases, followed by those between 1 month- 1 year, and the rate declined progressively with age groups.

The metabolic disorders diagnosed were, as shown in tables 2, amino acid disorders 86 (4.9%) ,the most frequent among the them was homocystinuria HCY 36(2%) , the next was pheylketonuria PKU 19 (1%) ,tyrosimemia TYR.14(0.8%) and maple syrup urine disease MSUD13(0.74%).

Mitochondrial disorders (fatty acids oxidation disorders and organic acidemias)were36(2%) , The most common fatty acid oxidation defect was the medium chain acyle co A dehydrogenase deficency (MCAD) 7(0.4%) ,and among the organic acidemias the most frequent was the methylmalonic academia (MMA) 7(0.4%) .

Thirty one cases(1.76%) of galactosemia were diagnosed. Glucose 6phosphate dehydrogenase deficiency 66 (3.75%). Five cases were proved to be hypothyroid and one case of biotinidase deficiency. As genetic analysis is not available in the country yet, the results represent preliminary data of both the clinical and MS/MS findings.

The above diagnosis lacked genetic analysis, due to the unavailability of these facilities, so the diagnosis relied on clinical and biochemical evaluation. One hundred seventy four (9.8%) cases had positive consanguineous marriage between father and mother ,while 132(7.5%) cases had positive history of a similar condition in the family or history of sudden infant death.

III. Discussion

Metabolic disorders are individually rare but collectively they represent a significant percentage of children and infants that present with acute problems. A high index of suspicion is most important in making the diagnosis. Successful emergency treatment depends on early diagnosis (18,19,20). Early screening and diagnosis may help to decrease mortality and morbidity rates in children with IEM.

In this study, a total number of symptomatic Iraqi children of 1758, from birth to early adolescence , were analyzed for possible IEM, positive cases were 224 /1758 ,with a rate of detection(12.7%). In comparison, Huang et al(21) from China [2012], analyzed 11,060 symptomatic patients for metabolic diseases, with the same age range,62 cases were diagnosed with IEM, with a detection rate of only 0.56%, however several other Chinese studies (22,23,24), reported a detection rate of 3.2%,6.6% and 9.5% respectively. The wide variation in detection rates is not surprising, given the different screening criteria for IEM used in different countries, the inconsistent sample-collection methods, and probably the difference in the rate of consanguinity.

Among the 62 cases in Huang study(21) ,amino acid disorders came first (43.5%), this agrees with our results, where amino acids disorders were 86 cases(36.3%)out of the positive cases and 4.9 % out of the total number ,this also agreed with Vilarinho L et al and Yoon HR et al(6,24), who carried similar studies on newborns and on symptomatic children in Portugal and South Korea.

In our study homocystinuria came first in its incidence among amino acids disorders 36(2%)from of the total studied group, a Qatari study that showed the incidence of homocystinuria in Qatari population to be 1:1,800, the highest in the world, and about 6% of the Qatari population were carriers for this condition (25).

In the Iraqi sample, homocystinurea was followed by phenylketonuria 19(1%), tyrosinemia14(0.8%) and maple syrup urine disease 13(0.74%). While with Huang et al (21), Vilarinho L et al(6) and Yoon HR et al (24) studies , phenylketonuria came first followed by maple serum urine disease. A similar distribution was seen in a study from south Iran (26) in which selective screening of PKU, MSUD and tyrosinemia was carried out, where 1044 children were investigated , revealing PKU 43 cases (4.1%), tyrosinemia 15 cases (1.4%) and MSUD 6 cases (This study did not include homocystinurea in the screening).

In the current study, fatty acid oxidation defects(FAO) came second in frequency 20(1.1%) to aminoacid disorders , followed by the organic acidemias16(0.9%) ,while the reverse was seen in Huang et al study (21) and in a Bahraini study (27), where organic acidemias found in 41.9% and 44% of the analyzed cases respectively, followed by FAO disorders in 14.5% and 36% of the cases in those two studies.

In Huang et al(21) study consanguinity was very infrequent ,just one family(1.6%), and a family history of IEM was reported in three patients (4.8%). While in our study 174 (9.9%) of them had positive consanguineous marriage, one hundred thirty two (7.5%) of diagnosed patients had positive family history of either metabolic disorders or sudden unexplained death of siblings ,this can be explained by highly frequent consanguineous marriage in our society(14) , an incidence that is almost the same with that in an Iranian study(26), and even more in the Bahrani study (27), where 21/25 cases came from first degree cousins.

In a Saudi study (30) to investigate the prevalence of consanguineous marriages, (57.7%) of the Saudi families screened were consanguineous. This study also showed the prevalence of consanguinity in Arab region as following in United Arab of Emirates (61.6%) , in Iraq (57.9%) , in Kuwait (54.3%) , in Jordan (50.23%) , in Bahrain (39.4%) , and in Egypt (28.96%) .

In a study from Egypt (31), G6PD deficiency was demonstrated in 11.4% of a sample of 70 neonates with prolonged jaundice, while it was documented in 66(3.75%) of our studied cases(as G6PD was essayed in all the samples, regardless of their complaint)

In conclusion, amino acids disorders, G6PDD and fatty acids oxidation disorders were the most common metabolic disorders in our Iraqi study, incidence and types of prevalent IEM differ in different countries, implying the necessity to carry out such surveys preparing for disease selection for neonatal screening programs.

A positive consanguinityy and positive family history played an important role in evolution of the suspicion & early picking up of suspected cases for selective screening & diagnosis .Iraq being one of the highest regarding the rate of consanguinity, and is expected to show a higher prevalence of IEM. Lastly, genetic analysis is an important issue in fulfilling the diagnosis of inherited IEMs, we hope active steps will be taken to start such investigations.

Age distribution	Number of patients and % .from Total number of patients 1758(100%)
Neonates (birth -30 days)	164(9.3%)
Infants (> 30 days -1 yr)	823(46.8%)
Preschool Ages (> 1 yr –5 yrs)	606(34%)
School Ages (> 5 yrs)	165(9.3%)
Positive consanguineous marriages	174(9.8%)
Patients had positive family history of either metabolic disorders or sudden unexplained	132(7.5%)

death of siblings	

Table (1):-the distribution total analyzed patients according to age. Incidence of consanguinity and positive family history.

Disease name	Number of cases
Amino acid defects	86(4.9%)
HCY(homocystinuria)	36(2%)
PKU(phenylketonuria)	19(1%)
TYR(tyrosinemia)	14(0.8%)
MSUD(maple serum urine disease)	13(0.74)
NKHG(nonketotichyperglycinemia)	1
HPA(hyperphenylalaninemia)	1
(urea cycle defects)	1
Fatty acids defects	20(1.1 %)
MCAD(medium chain acyle co A dehydrogenase deficiency)	7(0.4%)
CUD(carnitine uptake defect)	4(0.2%)
VLCAD(very long chain acyle co A dehydrogenase deficiency	3(.0.17%)
CPT-I(carnitinepalmitoyltransferase I deficiency)	3
SCAD (short chain acyle co A dehydrogenase deficiency)	2
CPT-II(carnitine palmitoyltransferase II deficiency)	1
Organic acid disorders	1(0.05%)
MMA(methyl malonic academia)	7(o.4%)
BKT(betaketothiolase deficiency)	3
PA(propionic academia)	3
IVA(isovaleric academia)	2
Biotidinase (elevated C5OH)	1
Carbohydrates defects (Galactosemia)	31(1.76%)
CH(congenital hypothyroidism)	5 (0.28%)
G6PD(glucose 6 phosphate dehydrogenase deficiency)	66(3.75%)
Total number of IEM cases	**224(12.7%)/1758**

Table (2):-The individual diagnosed disorders of IEM.

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