Preliminary results of neonatal screening of 19 genetic and metabolic disorders in Qalyubia Governorate

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Abstract

Background:, Expanded newborn screening for IEMs by tandem mass spectrometry (MS/MS) is an efficient approach for early diagnosis and presymptomatic treatment to prevent severe permanent sequelae and death.

Aim: to detect the prevalence of the preventable 19 IEM screened among neonates in NICUs of our community and identify types of IEM mostly commonly found in Qalyubia Governorate. Screening obstacles are also addressed to be resolved appropriately with provision of purposeful family counseling.

Methods: This cross-sectional study was performed on neonates admitted to NICU of Benha Children Hospital in Qalyubia Governorate for early detection of 19 neonatal genetic diseases and early treatment of positive ones for duration of one year from june 2022:june 2023. This study included 700 neonates.All neonates subjected to detailed history taking , detailed examination and assessment of 19 genetic and metabolic disorders.

Results: Regarding the screening test for 19 genetic and metabolic disorders of the studied group, 19 (2.71%) patients were true positive, 51 (7.29%) patients were false positive, and 630 (90%) patients were negative . Congenital adrenal hyperplasia was confirmed in 1 (0.14%) patient, G6PD enzyme deficiency was confirmed in 16 (2.29%), and urea cycle defect was confirmed in 1 (0.14%) patient and elevated TSH and confirmatory free T4 recommended was found in 1 (0.14%) patient**.** Regarding the outcome of the positive cases, 18 (94.74%) patients survived, and 1 (5.26%) patient did not survive (urea cycle defect).

The diagnostic accuracy of the screening test was 92.7%, with 100% sensitivity, 92.5% specificity, 27.1% PPV and 100% NPV. This test was proven to be an effective and good negative test.

Conclusion. This test was proven to be an effective and good negative test. Infants who screened positive for diseases were managed early even before they were symptomatic. Therefore, it could prevent or revert severe disabilities and reduce health care costs .

Key words: newborn screening, inborn errors of metabolism, incidence of IEMs

1. Introduction

Newborn screening, for the detection of inborn errors of metabolism (IEM), has long been recognized as an essential, life-saving, and effective preventive public health service. In other instances, identifying newborns with a disorder means that they can be treated and thus not face life long disability or cognitive impairment. with the advent of this new screening technology, babies can be tested-and treated- for many more disorders than was previously possible **(1)**

Inborn errors of metabolism (IEMs) are a large group of monogenic diseases resulting in death and abnormalities of physical and neurological development at almost all stages of life. IEMs are always caused by the defect of an enzyme, its coenzyme or a transporter leading to the accumulation of its substrate and or the insufficiency of its downstream products. The introduction of tandem mass spectrometry (TMS) allows

screening for more than 50 IMEs using dried blood spot in the neonatal period [(2)].

Neonatal screening started worlded wide in the early 1960s [(3)]

In the early 1990s there was a revolution in NBS programms which aimed mainly at the detection of amino acid organic acid and mitochondrial fatty acid-oxidation disorders [(4)].So the aim of this study is to detect the prevalence of the preventable 19 Inborn Error Of Metabolism (IEM) screened among neonates in NICUs of our community and identify types of IEM mosty commonly found in Qalyubia Governorate. Screening obstacles are also addressed to be resolved appropriately with provision of purposeful family counseling.

2. Patients and methods

This cross-sectional study was performed on neonates admitted to NICU of Benha Children Hospital in Qalyubia Governorate from June 2022 to June 2023. This study included 700 neonates,

Inclusion Criteria

- Both males and females preterm and fullterm neonates admitted to NICU department of Benha Children Hospital in Qalyubia Governorate .
- The study complies with Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.
- The whole study design was approved by the local ethics committee, Faculty of Medicine, Benha University.

All neonates were subjected to the following:

1. Detailed history taking and general and local examination were performed
2. Assessment of 19 genetic and metabolic disorder

The newborn blood sample is obtained usually at 24 to 48 hours of life, and screening results are generally available within 24 hours. The test is performed by pricking the baby's heel to collect a few drops of blood. The blood is placed on a special type of paper and sent to a laboratory for analysis. (Martín-Rivada et al., 2021) These 19 genetic and metabolic disorder are congenital hypothyroidism ,Phenylketonuria,Tetrahydrobiopterin deficienc ,organic acidemia ,isovaleric acidemia ,propionic acidemia , methyl malonic acidemia , Maple syrup urine disease , tyrosinemia type I , homocystinuria , argininemia ,citrullinemia , ornithine transcarbamylase deficiency, fathy acid oxidation defect, biotinidase deficiency , congenital adrenal hyperplasia , galactosemia , cystic fibrosis and Glucose-6phosphate dehydrogenase deficiency.

Dried blood spots were pre-processed following the instruction of NeoBaseTM non-derivatized MS/MS kit), and then they were analyzed by using TQD tandem mass spectrometry system and NeoBase non-derivatized MS/MS kit.

Suspected positive cases were recalled for the repeated test by MS/MS. The follow-up testing commences for the second time positive cases, including biochemical tests or genetic analysis. The recall and follow-up protocol in the guidelines “Follow-Up Testing for Metabolic Disease Identified by Expanded Newborn Screening Using Tandem Mass Spectrometry” was applied in our study [(5)].

Definitive diagnosis is made by specialists based on the clinical symptoms, screening test, and biochemical and genetic analysis. The parents of all cases with definitive diagnosis were informed and referred to specialists for the treatment.

Statistical analysis:

Statistical analysis was done by SPSS v28 (IBM Inc., Armonk, NY, USA).

- Quantitative parametric data were presented as mean and standard deviation (SD). Quantitative non-parametric data were presented as median and interquartile range (IQR).
- Qualitative variables were presented as frequency and percentage (%).statistical significance is accepted when $p < 0,05$.

3. Results

Total number of studied group 700. Among the studied group, there were 147 (21%) cases had a positive history of previous neonatal death, 75 (10.71%) cases had a positive history of consanguinity, and all cases had a negative history of metabolic diseases in family except 11 (0.14%) case **(Table 1)** .

The most common causes of admission were jaundice in 180 (25.7%) cases, RDS in 175 (25%) cases, and respiratory distress in 168 (24%) cases Regarding the PT ranged from 10 – 40 seconds with a mean of 12.5 ± 2.12 seconds. INR ranged from 0.9 – 4 with a mean of 1.1 ± 0.31. The electrolyte results were NAD in all the studied cases except 1 (0.14%) case showed abnormality where Na level was 129 mEq/L and K level was 2 mEq/L. One case had PT level of 40s and INR of 4 **(Table 2)**

Regarding the screening test for 19 genetic and metabolic disorders of the studied group, 19 (2.71%) patients were true positive, 51 (7.29%) patients were false positive, and 630 (90%) patients were negative for the studied 19 genetic and metabolic disorders**.**

Concerning the confirmatory screening test for the 19 genetic and metabolic disorders, congenital adrenal hyperplasia was confirmed in 1 (0.14%) patient, G6PD enzyme deficiency was confirmed in 16 (2.29%), and urea cycle defect was confirmed in 1 (0.14%) patient and elevated TSH and confirmatory free T4 recommended was found in 1 (0.14%) patient. 681 (97.29%)patients were confirmed to be negative for the studied 19 genetic and metabolic disorders.**(Table 3)**

The majority of cases that were confirmed with G6PD enzyme deficiency were males 14 14 (73.68%), and only 2 (10.53%) were females. The confirmed case with congenital adrenal hyperplasia was a male 1 (5.26%), the confirmed case with urea cycle defect was a female 1 (5.26%), and also the confirmed case with elevated TSH and confirmatory free T4 was recommended, was a female 1 (5.26%).

Among the positive confirmed cases, 5 (26.32%) cases had a positive history of previous neonatal death, 7 (36.84%) cases had a positive history of consanguinity, and all of them had a negative history of metabolic diseases in family except 1 (5.26%) case. Additionally, no case had special character.**(Table 4)**

Regarding the outcome of the positive cases, 18 (94.74%) patients survived, and 1 (5.26%) patient did not survive (urea cycle defect).

The diagnostic accuracy of the screening test was 92.7%, with 100% sensitivity, 92.5% specificity, 27.1% PPV and 100% NPV. This test was proven to be an effective and good negative test.

4. Discussion

Most IEMs are serious diseases associated with significant morbidity and mortality, particularly in childhood. More than 700 IEMs are known to science, with a cumulative incidence of approximately 1 per 800 live births [(6)].

This study included 700 neonates, 59.1% were males and 40.9% were females. Among the studied group, The mean gestational age of the studied group was 36.7 ± 2.94 weeks, the mean age of admission was 4.3 ± 5.25 days, the mean weight was 2.5 ± 0.72 kg the most common causes of admission were jaundice in 180 (25.7%) cases, RDS in 175 (25%) cases, and respiratory distress in 168 (24%) cases followed by surgical causes (14.7%), sepsis (5.4%), and grower (2.1%) also **Al-Momani,** (2020) [7] 703 (56.4%) were male and 544 (43.6%) were female. Among those admitted, 776 (62.2%) were full term with the gestational age of ≥37 weeks; the remaining 471 (37.8%) were preterm with the gestational age <37 weeks. Most of the full-term neonates 576 (74.2%) had a normal weight (≥ 2500g) at time of admission, reported that the most common causes of the NICU admission were neonatal sepsis (n = 341; 27.3%), respiratory distress syndrome (RDS; n = 310; 24.9%), birth asphyxia (n = 163; 13.1%) and neonatal jaundice (10.7%).

In the current study Regarding the screening test for 19 genetic and metabolic disorders of the studied group, 19 (2.71%) patients were true positive, 51 (7.29%) patients were false positive, and 630 (90%) patients were negative for the studied 19 genetic and metabolic disorders. Concerning the confirmatory screening test for the 19 genetic and metabolic disorders, congenital adrenal hyperplasia was confirmed in 1 (0.14%) patient, G6PD enzyme deficiency was confirmed in 16 (2.29%), and urea cycle defect was confirmed in 1 (0.14%) patient and elevated TSH and confirmatory free T4 recommended was found in 1 (0.14%) patient. 681 (97.29%) patients were confirmed to be negative for the studied 19 genetic and metabolic disorders.

Our result run in accordance with Hassan et al., (2016) [5] who found 13 patients diagnosed with metabolic disorders, a total prevalence rate of 1:1944 (five cases with PKU, two with methylmalonic acidemia, two with isovaleric acidemia, and one case each of MSUD, propionic acidemia, β-ketothiolase deficiency, and primary carnitine deficiency). During the study period, 38 samples were flagged on initial screening (15/10,000), giving an initial false positive rate of 10/10,000. After the samples were repeated in duplicate only 31 remained flagged in at least two runs, and were recalled to the IMDU for clinical evaluation, giving a total recall rate of 12/10,000. Thirteen cases were confirmed and 18 cases were found to have non-significant elevations (7.3/10,000). True positive cases constituted 42% of those recalled.

The birth prevalence of metabolic disorders detectable by MS/MS varies greatly in different NBS studies. In the United States it ranges from 1:3367 in California (Feuchtbaum et al., 2012) to 1:4310 in North Carolina (Frazier et al., 2006). Most Northern European countries have a similar birth prevalence to the United States (e.g. Germany 1:3315) (Lindner et al., 2011). In Southern Europe it is higher (e.g. Italy 1:2105 (la Marca et al., 2008) and Spain 1:2060 (Couce et al., 2011)). The lowest reported birth prevalence is in the Far East (Taiwan 1:6219 (Niu et al., 2010) and Japan 1:9300 (Yamaguchi, 2008)), and the highest is in Arab nations, where consanguinity is much more common (Saudi Arabia 1:1381(Rashed et al., 1999) and Lebanon 1:1482 [8].

In the study by **Varghese et al., (2021)** [9], who studied the importance of early detection of genetic diseases, During the period of the

study from January 2018 to December 2018, a total of 7,027 newborns were tested in Dubai Health Authority facilities by the newborn genetic screening program (known as the "Step One Screening. Found that the incidence of screened disorders was 1:7,027 for congenital adrenal hyperplasia, 1:1,757 for congenital hypothyroidism, 1:1,757 for inborn errors of metabolism, 1:2,342 for biotinidase deficiency, 1:1,171 for hemoglobinopathies, 1:12 for hemoglobinopathy traits, and 1:10 for different genetic mutations of G6PD deficiency.

Zhang et al., (2020) [10], reported that 66 patients were biochemically diagnosed with IEMs. The total prevalence in the NICU was 1:640 (66/42, 257), included 46 cases of MMA (26 cases of isolated MMA and 20 cases of combined MMA/homocystinuria), 4 cases of propionic acidemia (PA), 3 cases of urea cycle disorders (UCD), 3 cases of maple syrup urine disease (MSUD), 2 cases of tyrosinemia (Tyr), 1 case of isovaleric acidemia (IVA), and 1 case of very long-chain acyl-CoA dehydrogenase deficiency (VLCADD).

Yang et al., (2018) [11] reported that from the results of further confirmatory tests, 56 out of the 1313 suspected cases were finally diagnosed with IEM. Among these 56 infants, 19 (1:5267) had amino acid disorders, 26 (1:3849) had organic acid disorders, and 11 (1:9098) had fatty acid oxidation disorders. Moreover, 54 of these individuals carried mutations, while the other 2 patients had argininemia.

Roy et al., (2020) [12], the positive screening results was for congenital hypothyroidism (CH) (n = 9), CAH (n = 15), and G6PD deficiency (n = 138)

The overall incidence of congenital hypothyrodism in our study was found to be 1:700, which is consistent with earlier studies that reported incidences ranging from 1:500 to 1:5,263 (Chen et al., 2013; Unnikrishnan & Vyas, 2017). A similar study in the United Arab Emirates showed an incidence of 1 in 1,873 for congenital hypothyroidism (Al Hosani et al., 2005). A study in Qatar showed an incidence of 1 in 3,152 (Lindner et al., 2007). The incidence across the world is described as 1 in 2,000 to 1 in 4,000 after the introduction of newborn screening (Multialam et al., 1994), which is lesser when compared with this study, this can be explained due to the relative small sample size in the current study.

Incidence of congenital adrenal hyperplasia (CAH) was 1;700 in our study, while, **Varghese et al., (2021)** [9], reported that incidence is 1 in 7,027 according to their study. A similar study by **Al Hosani et al., (2005)** [13] showed an incidence of 1 in 9,030 in the UAE. World-wide incidence of this disorder was estimated at 1:15,000 live births [14].

G6PD deficiency is the most common enzyme defect worldwide. G6PD is a manageable disorder which manifests primarily in males due to its X-linked pattern of inheritance. Heterozygous females, however, may be symptomatic due to a skewed degree of lyonization resulting in a red blood cell population that is largely deficient with respect to an active enzyme. Early detection will result in the prevention of clinical manifestation and aid physicians while counseling patients regarding contraindicated drugs, dietary restrictions, as well as avoidance of environmental factors that may trigger jaundice and kernicterus [12].

In the study by **Elella et al., (2017)** [15], who studied prevalence of glucose-

6-phosphate dehydrogenase deficiency in neonates in Egypt, Of 2782 screened newborns (1453 males and 1329 females), 2646 (95.1%) newborns were normal, 17 (0.6%) exhibited intermediate deficiency; 119 newborns (91 male newborns; 28 female newborns) were deficient for G6PD.

Moreover, a recent study by **Kassahun et al., (2023)** [16],reported G6PD deficiency was prevalent in 24.60% of African neonates with jaundice (95% CI:12.47–36.74) with considerable heterogeneity (I2 = 100%). Nigerian neonates with jaundice had the highest G6PD deficiency (49.67%), whereas South Africans had the lowest (3.14%).

In the current study, the majority of cases that were confirmed with G6PD enzyme deficiency were males 14 (73.68%), and only 2 (10.53%) were females. The confirmed case with congenital adrenal hyperplasia was a male 1 (5.26%), the confirmed case with urea cycle defect was a female 1 (5.26%), and also the confirmed case with elevated TSH and confirmatory free T4 was recommended, was a female 1 (5.26%).

This was in agreement with **Elella et al., (2017)** [15], who reported that the overall prevalence of G6PD deficiency of 4.3% with a male:female ratio of 3.2:1.

Similarly, **Javadi et al., (2022)**, [17] who reported that the pooled prevalence of G6PD deficiency among neonates with jaundice in Iran was 7.0% (95% CI: 5.5–8.5%). The results of subgroup analysis showed that, pooled prevalence of G6PD deficiency among male neonate (12.1%, 95%CI: 7.6–16.7%) was more prevalent that female (3.00%, 95%CI: 1.1–4.9%).

In the same way, **Al-Lawama et al., (2022)** [18], who found the overall prevalence of G6PD deficiency in our population was 1.44%, with a higher proportion among males than among females (2.38% vs. 0.36%), with a male-to-female ratio of 7:1.

G6PD deficiency belongs to an X-linked recessive inborn error of metabolism that largely affects males (hemizygosity), whereas heterozygous females can be of normal, intermediate or deficient G6PD activity due to random chromosome X inactivation, so this explain its higher prevalence in males [19] .

In the current study, Among the positive confirmed cases, 15 were males (78.9%), 5 (26.32%) cases had a positive history of previous neonatal death, 7 (36.84%) cases had a positive history of consanguinity, and all of them had a negative history of metabolic diseases in family except 1 (5.26%) case.

Recent years have seen a significant improvement in the NBS programs operating. However, there remains an urgent need to establish cost-effective screening procedures as well as efficient systems for quality control, patient recall, initiation of treatment, and follow-up. These measures along with effective counseling and communication with families regarding the benefits of NBS including diagnosis prior to clinical presentation, prompt treatment to prevent manifestation of symptoms, and consistent compliance with treatment and follow-up will result in successful execution of NBS programs. [20]

Therefore, it could prevent or revert severe disabilities and reduce health care costs. It will improve the quality of their lives by reducing complications, hospitalization, and subsequent morbidity and mortality. This emphasizes the importance of newborn screening despite the rarity of these conditions in a country like the Egypt where the rates of consanguinity is high. [21]

However, this study was limited due to the small sample size, which didn't allow for a better identification of the true prevalence of the preventable 19 IEM screened among neonates in NICUs of our community and identify types of IEM mostly commonly found in Qalyubia. The importance of newborn genetic screening has been emphasized in this study. Infants who screened positive for these diseases were managed early even before they were symptomatic

5. Conclusion

This test was proven to be an effective and good negative test. Infants who screened positive for diseases were managed early even before they were symptomatic. Therefore, it could prevent or revert severe disabilities and reduce health care costs. It will improve the quality of their lives by reducing complications, hospitalization, and subsequent morbidity and mortality. This emphasizes the importance of newborn screening despite the rarity of these conditions in a country like the Egypt where the rates of consanguinity is high.

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Table 1: Baseline characteristics of the studied group

		N=700
Gestational age (wks.)	**Mean ± SD**	36.7 ± 2.94
	Range	24 - 40
Age of admission (days)	**Mean ± SD**	4.3 ± 5.25
	Range	1 - 28
	Median (IQR)	2 (1-5)
History of previous neonatal death	**Positive**	147 (21%)
	Negative	553 (79%)
Consanguinity	**Positive**	75 (10.71%)
	Negative	624 (89.14%)
History of metabolic diseases in family	**Positive**	1 (0.14%)
	Negative	699 (99.86%)
Sex	**Male**	414 (59.14%)
	Female	286 (40.86%)
Weight (Kg)	**Mean ± SD**	2.5 ± 0.72
	Range	0.6 - 4.9
Weight (centile)	**Mean ± SD**	45.2 ± 20.52
	Range	5 - 97
Length (cm)	**Mean ± SD**	43.99 ± 6.48
	Range	29 - 52
Length (centile)	**Mean ± SD**	38.9 ± 19.79
	Range	5 - 90
Head circumference (cm)	**Mean ± SD**	30.25 ± 2.52
	Range	23 - 48
Head circumference (centile)	**Mean ± SD**	34.6 ± 20.06
	Range	5 - 97

IQR: interquartile range

This Table 1 shows that the baseline characteristics of the studied group..

Table 2: Cause of admission of the studied group and laboratory investigation of the studied group .

		N=700
Jaundice		180 (25.71%)
RDS		175 (25%)
Respiratory distress		168 (24%)
Surgical causes		103 (14.71%)
Sepsis		38 (5.43%)
Grower		15 (2.14%)
Cyanosis		9 (1.29%)
Hypoglycemia		6 (0.86%)
Hemorrhagic disease of newborn		5 (0.71%)
Epidermolysis bullosa		1 (0.14%)
		N=700
Hb (g/dL)	**Mean ± SD**	12.9 ± 1.83
	Range	9 - 20
HCT (%)	**Mean ± SD**	41.8 ± 7.21
	Range	6 - 61
TLC (*10^9/L)	**Mean ± SD**	11.2 ± 4.75
	Range	2.5 - 30.8
PLT (*10^9/L)	**Mean ± SD**	340.1 ± 137.69
	Range	33 - 768
CRP	**Positive**	244 (34.9%)
	Negative	456 (65.1%)
CRP (mg/dL)	**Mean ± SD**	26.7 ± 27.8
	Range	6 - 250
	Median (IQR)	12 (12-28)
PT (sec)	**Mean ± SD**	12.5 ± 2.12
	Range	10 - 40
INR	**Mean ± SD**	1.1 ± 0.31
	Range	0.9 - 4
Electrolyte	**NAD**	699 (99.9%)
	Abnormality	1 (0.14%)
	Na^+=129 mEq/L	
	K^+ = 2 mEq/L	

Table 3: The confirmatory screening test of the truly positive cases regarding sex

	True positive cases (n=19)	
	Male	**Female**
Congenital adrenal hyperplasia	1 (5.26%)	0 (0%)
G6PD enzyme deficiency	14 (73.68%)	2 (10.53%)
Urea cycle defect	0 (0%)	1 (5.26%)
Elevated TSH and confirmatory free T4 recommended	0 (0%)	1 (5.26%)

G6PD: glucose-6-phosphate dehydrogenase.

Table 4: Baseline characteristics of the positive confirmed cases

		N=19
Gestational age (wks.)	**Mean ± SD**	38.2 ± 0.9
	Range	37 - 40
Age of admission (days)	**Mean ± SD**	4.7 ± 6.18
	Range	1 - 25
	Median (IQR)	2 (1 - 5.5)
History of previous neonatal death	**Positive**	5 (26.32%)
	Negative	14 (73.68%)
Consanguinity	**Positive**	7 (36.84%)
	Negative	12 (63.16%)
History of metabolic diseases in family	**Positive**	1 (5.26%)
	Negative	18 (94.74%)
Sex	**Male**	15 (78.95%)
	Female	4 (21.05%)
Weight (Kg)	**Mean ± SD**	2.8 ± 0.4
	Range	1.9 - 3.2
Weight (centile)	**Mean ± SD**	46.1 ± 17.21
	Range	25 - 75
Length (cm)	**Mean ± SD**	46.8 ± 3.64
	Range	41 - 52
Length (centile)	**Mean ± SD**	43.7 ± 20.4
	Range	10 - 75
Head circumference (cm)	**Mean ± SD**	30.9 ± 1.39
	Range	29 - 33
Head circumference (centile)	**Mean ± SD**	35.3 ± 22.45
	Range	10 - 75

IQR: interquartile range