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Preliminary Results of Neonatal Screening of 19 Genetic and Metabolic Disorders in Qalyubia Governorate

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ABSTRACT

Background: Tandem mass spectrometry (MS/MS) expanded neonatal screening for inborn errors of metabolisms (IEMs) and it is an effective method for early diagnosis and presymptomatic therapy to avoid serious long-term consequences and mortality.

Objective: To detect the prevalence of the preventable 19 IEM screened among neonates in NICUs of our community and identify types of IEM most commonly found in Qalyubia Governorate. Screening obstacles were 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 to June 2023. This study included 700 neonates. All neonates were 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. Even before they showed symptoms, infants who were tested positive for illnesses were treated promptly. Thus, it might lower health care expenses and prevent or reverse serious disability.

Keywords: Newborn screening, IEMs, Incidence of IEMs**.**

INTRODUCTION

It has long been acknowledged that newborn screening, which looks for inborn errors of metabolism (IEM), is a crucial, life-saving, and efficient preventative public health service. With the introduction of this new screening technique, neonates may be tested for and treated for many more problems than was previously feasible. In other cases, diagnosing newborns with a condition implies that they can be treated and therefore not face lifelong handicap or cognitive impairment[(1)].

IEMs are a broad category of monogenic disorders that cause defects in neurological and physical development at practically every stage of life, as well as mortality. IEMs are always brought on by an enzyme, coenzyme, or transporter flaw that causes the substrate to build up or the downstream products to become insufficient. With the advent of tandem mass spectrometry (TMS), screening for over 50 IEMs throughout the newborn period is now possible utilising dried blood spots [(2)].

Neonatal screening started worldwide in the early 1960s [(3)]. In the early 1990s there was a revolution in NBS programmes which aimed mainly at the detection of amino acid organic acid, mitochondrial and fatty acid-oxidation disorders [(4)].

So, the aim of this study was to detect the prevalence of the preventable 19 IEM screened among neonates in NICUs of our community and identify types of IEM most commonly found in Qalyubia Governorate. Screening obstacles were also addressed to be resolved appropriately with provision of purposeful family counseling.

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 full-term neonates admitted to NICU Department of Benha Children Hospital in Qalyubia Governorate.

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 was obtained usually at 24 to 48 hours of life, and screening results were generally available within 24 hours. The test was performed by pricking the baby's heel to collect a few drops of blood. The blood was placed on a special type of paper and sent to a laboratory for analysis [(5)]. These 19 genetic and metabolic disorder were congenital

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hypothyroidism, phenylketonuria, tetrahydrobiopterin deficiency, organic acidemia, isovaleric acidemia, propionic acidemia, methyl malonic acidemia, maple syrup urine disease, tyrosinemia type I, homocystinuria, argininemia, citrullinemia, ornithine transcarbamylase deficiency, fatty acid oxidation defect, biotinidase deficiency, congenital adrenal hyperplasia, galactosemia, cystic fibrosis and Glucose-6phosphate dehydrogenase deficiency [(5)].

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

Suspected positive cases were recalled for the repeated test by MS/MS. The follow-up testing commenced 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 TMS" was applied in our study [(6)].

Specialists provided definitive diagnoses based on clinical symptoms, screening tests, and biochemical and genetic studies. The parents of all individuals with a clear diagnosis were notified and referred to professionals for treatment.

Ethical approval:

The whole study design was approved by the local Ethics Committee, Faculty of Medicine, Benha University. Informed written consent was obtained from parents of all participating children before recruitment in the study. The Helsinki Declaration was adhered to at every stage of the investigation.

Statistical analysis:

SPSS V. 28.0 was used for the statistical analysis. Using the Shapiro Wilk test, data were examined for normal distribution. Relative percentages and frequencies were used to display the qualitative data. Mean ± standard deviation (SD), range, median, and interquartile range were used to express quantitative data. Evaluation of diagnostic performance was performed by evaluation of the following: The diagnostic sensitivity: It measures the incidence of true positive results in patients' groups. Diagnostic specificity: It measures the incidence of true negative results in a non-diseased group. Positive predictive value (PPV): It is the percentage of true positive results among total positive results. Negative predictive value (NPV): It is the percentage of true negative results among total negative results.

RESULTS

Total number of the studied group was 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 1 (0.14%) case **(Table 1).**

Table (1): Baseline characteristics of the studied group

		N=700
Gestational age (weeks)	**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

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, it 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).**

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
HCT (%)	**Mean ± SD**	41.8 ± 7.21
TLC (*10^9/L)	**Mean ± SD**	11.2 ± 2.71
PLT (*10^9/L)	**Range**	33 - 768
	Median (IQR)	70 (70-145)
CRP	**Positive**	244 (34.9%)
	Negative	456 (65.1%)
CRP (mg/dL)	**Range**	6 - 250
	Median (IQR)	12 (12-28)
PT (sec)	**Mean ± SD**	12.5 ± 2.12
INR	**Mean ± SD**	1.1 ± 0.26
Electrolyte	**NAD**	699 (99.9%)
	Abnormality	1 (0.14%)
	Na^+ =129 mEq/L	
	K^+ = 2 mEq/L	

Range, median and IQR: Non parametric test.

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. The majority of cases that were confirmed with G6PD enzyme deficiency were males (14), and only 2 were females. The confirmed case with congenital adrenal hyperplasia was a male, the confirmed case with urea cycle defect was a female, and also the confirmed case with elevated TSH and confirmatory free T4 was recommended, was a female **(Table 3)**.

Table (3): The confirmatory screening test of the truly positive cases regarding the 19 genetic and metabolic disorders

	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.

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)**.

Table (4): Baseline characteristics of the positive confirmed cases

		N=19
Gestational age (weeks)	**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

Regarding the outcome of the positive cases, 18 (94.74%) patients survived. The diagnostic accuracy of the screening test was 92.7%, with 100% sensitivity, and 92.5% specificity. This test was proven to be an effective and good negative test (Tables 5, 6).

Table (5): Outcome of the positive confirmed cases

	N=19
Survived	18 (94.74%)
Not survived (urea cycle defect)	1 (5.26%)

Table (6): Diagnostic accuracy of the screening test for prediction of positive cases with genetic and metabolic disorders

	Diagnostic accuracy	Sensitivity	Specificity	PPV	NPV
Screening test	92.7%	100%	92.5%	27.1%	100%

PPV: positive predictive value, NPV: negative predictive value.

DISCUSSION

The majority of IEMs are dangerous illnesses that have high rates of morbidity and death, especially in young patients. Science has identified over 700 IEMs, with a combined frequency of around 1 in 800 live births [(7)].

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, and 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%). Additionally, **Al-Momani [(8)]** examined the patterns of admission and risk variables associated with newborn death. During the course of the study, 1,247 neonates were admitted to the NICU; of them, 703 (56.4%) were males and 544 (43.6%) were females. Of those hospitalised, 471 (37.8%) were preterm, meaning their gestational age was less than 37 weeks, and 776 (62.2%) were full term, meaning their gestational age was ≥37 weeks. The majority of full-term neonates, 576 (74.2%), had a normal weight of ≥ 2500 g when they were admitted. It was found that 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%) were the most common reasons for NICU admissions.

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 results run in accordance with **Hassan *et al.* [(6)]** who found 13 individuals with metabolic abnormalities were identified, representing a 1:1944 overall prevalence rate (two instances each of methylmalonic acidemia, isovaleric acidemia, propionic acidemia, and primary carnitine insufficiency, and five cases of PKU). 38 samples (15/10,000) were highlighted during the research period's initial screening, yielding an initial false positive rate of 10/10,000. Only 31 samples were highlighted in at least two runs after the samples were replicated in duplicate; these samples were then recalled to the IMDU for clinical review, yielding a recall rate of 12/10,000. 18 instances (7.3/10,000) with non-significant elevations were discovered, whereas 13 cases were verified. Forty-two percent of the recalled instances were true positives.

The newborn incidence of metabolic diseases detected by MS/MS differs significantly between NBS investigations. The greatest rates are in Arab countries, where consanguinity is substantially more widespread (Saudi Arabia 1:1381 and Lebanon 1:1482) [(9)].

In the study by **Varghese *et al.* [(10)]**, who studied the significance of genetic illness early identification, A total of 7,027 infants were tested in Dubai Health Authority facilities between January and December 2018 as part of the newborn genetic screening programme, also known as the "Step One Screening". Congenital adrenal hyperplasia had an incidence of 1:7,027 for screening disorders, congenital hypothyroidism had an incidence of 1:1,757 for IEM, biotinidase deficiency had an incidence of 1:2,342, hemoglobinopathies had an incidence of 1:1,171 for hemoglobinopathy traits, and various genetic mutations of G6PD deficiency had an incidence of 1:10.

Zhang *et al.* [(11)], reported that IEMs were identified biochemically in 66 individuals. 46 cases of mixed muscle disorders (MMA) (26 isolated cases and 20 combined cases with 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) were among the overall prevalence in the NICU, which was 1:640 (66/42, 257).

Yang *et al.* [(12)] reported that from 56 out of the 1313 suspected patients had an IEM diagnosis after additional confirming testing. Of these 56 newborns, 26 (1:3849) had abnormalities related to organic acids, 11 (1:9098) to fatty acid oxidation, and 19 (1:5267) to amino acid diseases. Additionally, two of the patients had argininemia, and 54 of the people had mutations.

Roy *et al.* [13], a total of 13,376 newborns were examined; of them, nine had positive screening findings for congenital hypothyroidism (CH), fifteen for CAH, and one hundred and thirty-eight for G6PD deficiency.

In our investigation, the total incidence of congenital hypothyroidism was determined to be 1:700. Congenital hypothyroidism has an incidence of 1 in 1,873 according to a comparable research conducted in the United Arab Emirates [14].

Our study found that the incidence of congenital adrenal hyperplasia (CAH) was 1;700, whereas **Varghese *et al.*'s** [10], investigation indicated that the incidence is 1 in 7,027. **Al Hosani *et al.*** [14] found that the incidence in the United Arab Emirates was 1 in 9,030. The estimated global incidence of this disease was 1 in 15 live births [15].

Globally, G6PD insufficiency is the most prevalent enzyme defect. G6PD is a treatable condition that mostly affects men because of its X-linked inheritance pattern. However, a skewed degree of lyonization that leaves the red blood cell population mostly lacking in an active enzyme may cause symptoms in heterozygous females. Early identification can let clinicians educate patients about food limitations, avoidance of environmental variables that may cause jaundice and kernicterus, and contraindications to medications, thereby preventing clinical manifestation [13].

Elella *et al.* [16] studied the incidence of glucose-6-phosphate dehydrogenase insufficiency of the newborns in Egypt. Among the 2782 neonates (1453 males and 1329 females) that were screened, 2646 (95.1%) were normal, 17 (0.6%) showed an intermediate deficit, and 119 (91 males and 28 females) were deficient for G6PD.

Moreover, a recent study by **Kassahun *et al.*** [17], reported that with significant heterogeneity (I2 = 100%), G6PD deficiency was common in 24.60% of African newborns with jaundice (95% CI:12.47–36.74). G6PD insufficiency was highest in Nigerian newborns with jaundice (49.67%) and lowest in South African neonates (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 (5.26%), the confirmed case with urea cycle defect was a female (5.26%), and also the confirmed case with elevated TSH and confirmatory free T4 was recommended, was a female (5.26%).

This was in agreement with **Elella *et al.*** [16], who reported that the male to female ratio was 3.2:1 and the overall frequency of G6PD deficiency was 4.3%.

Similarly, **Javadi *et al.*** [18] who reported that among Iranian newborns with jaundice, the pooled prevalence of G6PD deficiency was 7.0% (95% CI: 5.5–8.5%). Subgroup analysis findings revealed that the pooled prevalence of G6PD deficiency was higher in male neonates (12.1%, 95%CI: 7.6–16.7%) than in female neonates (3.00%, 95%CI: 1.1–4.9%).

In the same way, **Al-Lawama *et al.*** [19], who found in our population that the percentage of people who lack G6PD was 1.44% overall. The male-to-female ratio was 7:1, with a larger percentage of males than females (2.38% vs. 0.36%).

The X-linked recessive inborn error of metabolism known as G6PD deficiency primarily affects males (hemizygosity). On the other hand, heterozygous females may have normal, intermediate, or deficient G6PD activity as a result of random X chromosome inactivation, which explains why G6PD deficiency is more common in males [20].

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.

The way that NBS programmes are run has significantly improved in recent years. Still, there is a pressing need to develop affordable screening protocols and effective methods for quality assurance, patient recall, therapy start, and follow-up. NBS programmes will be executed successfully if these steps are taken in addition to providing families with good counselling and information about the advantages of NBS, such as diagnosis before clinical presentation, early treatment to prevent symptom manifestation, and regular adherence to treatment and follow-up [21].

Thus, it might lower health care expenses and prevent or reverse serious disability. By lowering problems, hospitalisation, and the ensuing morbidity and mortality, it will enhance their quality of life. This highlights the need of screening newborns even in countries like Egypt where rates of consanguinity are high and certain illnesses are uncommon [22].

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. This study highlights the value of genetic screening for newborns. Even before they had symptoms, infants who tested positive for these illnesses were treated promptly.

CONCLUSION

This screening test was proven to be an effective and good negative test. Even before they showed symptoms, infants who were tested positive for illnesses were treated promptly. Thus, it might lower health care expenses and prevent or reverse serious disability. By lowering problems, hospitalisation, and the ensuing morbidity and mortality, it will enhance their quality of life. This highlights the need of screening newborns even in countries like Egypt where rates of consanguinity are high and certain illnesses are uncommon.

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