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ORIGINAL ARTICLE

OVERVIEW OF DUHOK/IRAQ PROJECT OF EXPANDED NEWBORN SCREENING

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Summary

Background: Newborn screening is a public health prevention system that intends to detect, early in life, a group of serious diseases that require early intervention. Institutionalizing and sustaining this system presents a remarkable challenge in developing public health systems. Duhok project for expanded newborn screening started in June 2018 with a panel of seven diseases including phenylketonuria (PKU), Galactosemia (GAL), congenital hypothyroidism (CHT), Cystic fibrosifcardiacs (CF), Congenital adrenal hyperplasia (CAH), G6PD deficiency and biotinidase deficiency. In the next few years, the panel expanded to include, finally, 72 tests, to detect various disorders of amino acids, fatty acid oxidation, organic acid, lysosomal storage disease, immunodeficiency, spinal muscular dystrophy, and others.
Objectives: To evaluate the Duhok project of expanded newborn screening.
Methods: In a retrospective cross-sectional study conducted between June 2018 and 31 November 2021, a total of 3872 newborns were screened from 8 governorates of Iraq and the Kurdistan region. Heel prick dry blood spot samples were obtained from all newborns for biochemical and immunoassay testing.
Results: A total of 527 cases were detected, frequently detected disorders were Glucose 6 phosphate dehydrogenase deficiency, cystic fibrosis, congenital adrenal hyperplasia and phenyl ketone urea. Most of the positive cases (66%) were older than 7 days at screening.
Conclusion: The article highlights the overview of the expanded newborn screening project in Duhok/Iraq. NBS has not yet become prevalent in Iraq, thus the screening for metabolic disorders is not normally requested until a patient is already experiencing symptoms.

Key words: an overview of expanded newborn screening; Newborn Screening Program; Duhok

Introduction

Since the early 1960s, when monitoring for phenylketonuria (PKU) using the "Guthrie test," invented by Robert Guthrie, commenced, neonates are screened for metabolic diseases (1). Later, many newborn-screening schemes included tests for sickle cell hemoglobinopathies, galactosemia, and congenital hypothyroidism had been established. Nevertheless, samples are taken using the same blood spot technique. With the introduction of “tandem mass

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spectrometry (MS/MS)", we are now able to recognize aberrant analytes linked to several metabolic illnesses involving amino acids, organic acids, and fats. Given the advancements in newborn screening, the primary care physician can now be the initial point of contact for families whose children receive aberrant results by being aware of the range of testing and the advised confirmatory follow-up (2).

There are recommendations for a core panel of conditions that fit the requirements for screenings as a consequence of the neonatal screening's work. The following are the considerations for screening with the right sensitivity and specificity test:

It may be identified at an early age when it may not have been medically recognized, and there are positives to early diagnosis, prompt intervention, and appropriate treatment of the illness being evaluated (2).

Paediatricians and family practitioners should be ready to help parents in understanding the screening procedure, diagnostic procedures, and indicators as well as the potential repercussions of an inconclusive neonatal check. It might be reassuring for parents if the primary healthcare provider is aware of the genetic services available to aid in treatment and diagnosis (3).

Families who complain about newborn screening frequently express worries about their primary care doctor's ignorance regarding their baby's metabolic condition (4).

Over 98% of the 4 million or more babies in the United States get screened every year. Newborn screening offers the chance for therapy and substantial decreases in morbidity and mortality via earlier detection (5, 6). Over 7.6 million babies worldwide are delivered each year with genetic or congenital disorders, with mid- and reduced nations accounting for 90% of these deliveries (7).

The programme of newborn screening test serve over 7 million newborns annually, in countries which are considered with highest rate of consanguineous marriage. Hence, the Middle East and North Africa (MENA) programme cover 4000 kilometres (17 nations) providing these screening test for up to 300 million people. According to various research, MENA countries have a higher frequency of hereditary metabolic and endocrine problems than Western nations. Early detection and treatment of these illnesses can lower illness and death, although newborn screening (NBS) is sometimes infrequently carried out in these areas (8).

Only a tiny number of MENA countries, accounting for 12.2% of regional births, have widespread newborn prevention strategies for a variety of illnesses, according to published statistics on MENA NBS programmes. Several areas only check for a few conditions in certain segments of the population (8).

The incidence of heritable disorders in the MENA region is probably underreported due to inadequate availability of statistics (8). However, testing services have only been capable of covering a small number of illnesses in very many nations due to a lack of funding to grow. The necessity for a well-established organization for screening and expenditures are a couple of the factors contributing to these countries' low testing rates for certain illnesses (9). The healthier living condition of individuals who receive prompt diagnosis and appropriate treatment is a benefit of routine screening. False positive findings can increase expenditures, cause worry for parents, and postpone detection in undetected cases, among other detrimental consequences of routine screening (10).

Recently Iraqi Ministry of Health (MOH) has paid great interest in screening test for newborns raising the logo of "society free of disease" and this has encouraged the establishment of programs needed to achieve this goal (11).

Iraq, Duhok project of expanded newborn screening:

The Newborn Screening Program was launched as a pilot study in April 2013 with Baghdad and Karbala being the initial provinces. The preliminary design stage has been concentrated on technical assistance for further than one year, introducing the much more recent technology for early diagnosis of two assigned inborn errors of metabolism, "phenylketonuria (PKU), galactosemia (GAL)", and also rare "genetic hypothyroidism (CHT)", by testing blood from a baby's heel prick (12).

Duhok project for expanded newborn screening started in June 2018 with a panel of seven tests including "phenylketonuria (PKU), Galactosemia (GAL), congenital hypothyroidism (CHT), Cystic fibrosis (CF), Congenital adrenal hyperplasia (CAH), G6PD deficiency and biotinidase deficiency". In march 2020 the panel expanded to 63 tests, including amino acid disorder, fatty acid disorders and organic acid disorders (2).

In December 2020 the expanded panel of NBS upgraded to 69 tests, including "six lysosomal storage diseases (LSD); Gaucher Disease, Mucopolysaccharide Disease Type I (MPS I), Pompe Disease, Fabry Disease, Krabbe Disease, and Niemann-Pick Disease". Recently in September 2021 Spinal Muscular Atrophy SMA, Severe Combined Immunodeficiency SCID X-Linked Agammaglobulinemia XLA were added to the expanded newborn screening panel. The upgraded NBS expanded panel will include 72 tests. With this update, Expanded NBS Panel will be one of the most comprehensive NBS panels in the world. Additionally, all these tests are performed by the most reliable machines and kits in the world.

The final version of the Duhok project of expanded newborn screening covers all the following groups of diseases: "Amino acid disorders, fatty acid oxidation disorders, organic acid disorders, endocrine disorders, haematological disorders, lysosomal storage diseases (Gaucher Disease, Mucopolysaccharide Disease Type I (MPS I), Pompe Disease, Fabry Disease, Krabbe Disease, and Niemann-Pick Disease), Spinal Muscular Atrophy SMA, Severe Combined Immunodeficiency SCID, X-Linked Agammaglobulinemia XLA, and Miscellaneous diseases" (2, 4, 8) (Table 1).

Patients and methods

Design: Retrospective Cross-sectional study.

Duration: From Jane 2018 – November 2021.

Setting: Iraq/ Duhok/ AmrLab Medical Laboratories.

Sample Collection:

Blood specimens from a neonatal heel prick is usually collected 2-14 days after birth (samples should be collected no less than 24 hours following the baby's 1st milk feeding if full-term). If the neonate is premature the blood is usually collected 5-7 days after birth.

Blood specimen should be collected directly from the heel prick onto the filter paper that is FDA specified for sample collection (Avoid EDTA in all conditions). Minimally 6 circles for NBS (expanded). Always check the back of the filter paper to confirm the complete filling of the circle.

Patients information

Before sample collection, be sure that the required information on the specimen card has been completed, including, given name, address, parents' name, gender, date of birth, date of specimen collection, birth weight, technician collected the samples, referral physician (13).

The recommended collection technique is as follows:

Preparation of sample collection spots by cleaning/warming the baby's heel, drying the swab spot, puncturing the infants' heel, wipe the blood drop by gentle touch with filter paper sufficiently on the printed area for each test that both side of filter paper penetrated with blood, and finally air-dry specimen horizontally (14).

Specimen Rejection Criteria (To avoid faulty assay results):

Insufficient sample, abraded sample, non-properly dried sample, supersaturated sample, diluted sample, discolored sample, contaminated sample, serum rings, and clotted or layered sample (15).

Table 1. The panel of tests for Screening.

Amino Acids
Alanine (Ala)
Arginine (Arg)
Argininosuccinic acid (ASA)
Citrulline (Cit)
Glutamine/Lysine (Gln/Lys
Glutamic acid (Glu)
Glycine (Gly
Leucine/Isoleucine/Hydroxyprolin (Leu/Ile/Pro-OH)
Methionine (Met)
Ornithine (Orn)
Phenylalanine (Phe)
Proline (Pro)
Tyrosine (Tyr
Valine (Val)

Ketones
Succinylacetone (SA)

Nucleosides
Adenosine (ADO)
2'-deoxyadenosine (D-ADO)

Lysophospholipids
C20:0 lysophosphatidylcholine (C20:0-LPC)
C22:0 lysophosphatidylcholine (C22:0-LPC)
C24:0 lysophosphatidylcholine (C24:0-LPC)
C26:0 lysophosphatidylcholine (C26:0-LPC)

Lysosomal Enzymes
Acid-Beta-glucocerebrosidase (ABG)
Acid-sphingomyelinase (ASM)
Beta-galactocerebrosidase (GALC)
Alpha-L-iduronidase (IDUA)
Alpha-galactosidase A (GLA)
Acid-alpha-glucosidase (GAA)

Primary Immunodeficiency (SCID and XLA)
TREC (T-cell receptor excision circles)
KREC (Kappa-deleting recombination excision circles)

Spinal Muscular Atrophy
SMN1 exon 7

Carnitine
Free carnitine (C0)
Acetylcarnitine (C2)
Propionylcarnitine (C3
Malonylcarnitine/3-OH-butylcarnitine (C3DC/C4OH)
Butylcarnitine (C4)
Methylmalonyl/3-OH-isovalerylcarnitine (C4DC/C5OH)
Isovalerylcarnitine (C5)
Tiglylcarnitine (C5:1)
Glutarylcarnitine/3-OH-
hexanoylcarnitine (C5DC/C6OH)
Hexanoylcarnitine (C6)
Adipylcarnitine (C6DC)
Octanoylcarnitine (C8)
Octenoylcarnitine (C8:1)
Decanoylcarnitine (C10)
Decenoylcarnitine (C10:1)
Decadienoylcarnitine (C10:2)
Dodecanoylcarnitine (C12)
Dodecenoylcarnitine (C12:1)
Tetradecanoylcarnitine (Myristoylcarnitine) (C14)
Tetradecenoylcarnitine (C14:1)
Tetradecadienoylcarnitine (C14:2)
3-OH-tetradecanoylcarnitine (C14OH)
Hexadecanoylcarnitine (Palmitoylcarnitine) (C16)
Hexadecenoylcarnitine (C16:1)3-OH-hexadecanoylcarnitine (C16OH)3-OH-hexadecenoylcarnitine/Heptadecanoylcarnitine (C16:1OH/C17)
Octadecanoylcarnitine (Stearoylcarnitine) (C18)
Octadecenoylcarnitine (Oleylcarnitine) (C18:1)
Octadecadienoylcarnitine (Linoleylcarnitine) (C18:2)
3-OH-octadecanoylcarnitine (C18OH)
3-OH-octadecenoylcarnitine (C18:1OH)
3-OH-octadecadienoylcarnitine (C18:2OH)
Eicosanoylcarnitine (Arachidoylcarnitine) (C20)
Docosanoylcarnitine (Behenoylcarnitine) (C22)
Tetracosanoylcarnitine (Lignoceroylcarnitine) (C24)
Hexacosanoylcarnitine (Cerotoylcarnitine) (C26)

Others
Total Galactose, Blood Spot
TSH, Blood Spot
G6PD, Blood Spot
Immunoreactive Trypsin IRT, Blood Spot
17a-OH-progesterone, Blood Spot
Biotinidase, Blood Spot
Acid-alpha-glucosidase (GAA)

Duhok Expanded Newborn Screening Practical Regulations:

- Each location should have one “contact person” concerning the NBS.
- Each location will receive Filter Papers with a specific code on them.
- They can collect specimens at any time.
- Minimally 6 circles for NBS (expanded). Always check the back of the filter paper to confirm the complete filling of the circle.
- After collection, leave the filter paper at Room Temperature for 3 hours to dry.
- After dryness, put filter paper, in an envelope, in a closed box, and put it in a fridge.
- Locations can transport specimens Dried Blood Spot (DBS) to the centre at any time (daily, twice weekly, or weekly, based on the desire of the location).
- The results (TAT): From 5 – 10 days (after the arrival of specimens to the centre). In general, we will depend on the "Calling System", and there will be continuous direct contact with "the contact person" to notify us about the abnormal results.
- Abnormal results will be repeated on the same specimen with no extra fee; If still abnormal then the “report’ will be issued and the centre will call the "contact person" to notify the physician in charge immediately and to request repeating sampling for further confirmation (to eliminate the possibility of identification errors, and to confirm by other methods). The required sample will be DBS with/without other kinds of samples (according to the test to be repeated and will be clarified clearly in the report and by phone). The performance of NBS tests on the second sample will also be free of charge. But if other confirmatory tests (e.g Genetic test for Cystic Fibrosis) are requested, then there will be an extra charge (will be detailed by call).

Sample size: The number of infants screened in the Duhok expanded NBS project from June 2018 – November 2021 was 3872. These samples are obtained from various Iraqi cities, mainly from Duhok, Baghdad, Mosul, Karbala, Erbil, Kirkuk, Diyala, and Sulaimanyia through communication and collaboration with medical laboratories and paediatricians in these cities.

Results

Table 2 illustrate the number of screened newborns according to the years of screening; the total number of screened newborns was 3872.

Table 2. The number of screened newborns according to the year o screening.

year	Screened babies
2018	333
2019	1338
2020	1016
2021	1185
Total	3872

Table 3 Clarify the distribution of screened newborns according to location.

Table 3. The distribution of expanded NBS according to locations.

Location	Expanded NBS
Duhok	2401
Baghdad	900
Mosul	202
Karbala	103
Erbil	88
Kirkuk	65
Diyala	63
Sulaimania	50
Total	3872

Table 4 illustrates the clinical cases diagnosed by the expanded newborn screening program.

Table 4. The clinical cases diagnosed by expanded newborn screening.

Clinical condition	Analyte	No	%
G6PD Deficiency	G6PD Enzyme	260	6.715
Cystic Fibrosis	IRT	78	2.014
Congenital Adrenal Hyperplasia	17-OH Progesterone	50	1.291
PKU	Phenylalanine	37	0.956
Biotinidase Deficiency	Biotinidase Enzyme	30	0.775
Hypothyroidism	TSH	12	0.310
MSUD	Leu\Ile\Pro-OH	11	0.284
Propionic Acidemia (PA) or Methylmalonic Aciduria (MMA)	C3	7	0.181
Mitochondrial diseases or malonic acidemia	C3DC/C4OH	4	0.103
SCID	TREC	4	0.103
Galactosemia	GAO	3	0.077
C5 Isovaleric Acidemia (IVA)	C5	3	0.077
HMG-CoA Lyase Deficiency or (3-MCC) or (3MGA)	C4DC/C5OH	2	0.052
Glutaric Aciduria Type I (GA I)	C5DC/C6OH	2	0.052
Multiple Acyle-CoA Dehydrogenase deficiency (MAD)	Methionine	2	0.052
TPN	Alanine	2	0.052
Citrullinemia	Citrulline	2	0.052
Homocystinuria	Methionine	2	0.052
XLA	KREC	2	0.052
Mucopolysaccharidosis type I (MPS I)	IDUA	1	0.026
Isobutyryl Aciduria (IBD) or Short Chain Acyl Co-A Dehydrogenase Deficiency (SCAD)	C4DC/C5OH	1	0.026
OTC Ornithine Transcarbamylase	Citrulline	1	0.026
liver failure or Homocystinuria	Methionine	1	0.026
Beta Ketothiolase Deficiency	C5:1	1	0.026
Lysosomal Storage Disorders	GAA	1	0.026
ADA-SCID	D-ADO	1	0.026
M/SCHAD	C3DC/C4OH	1	0.026
Carnitine Uptake/Transport Deficiency (CUD)	C0	1	0.026
Methylmalonic aciduria	C3	1	0.026
HMG-CoA Lyase Deficiency	C5DC/C6OH	1	0.026
Carnitine palmitoyltransferase (CPT2) deficiency	GALC	1	0.026
Hyperbilirubinemia	Citrulline	1	0.026
Krabbe disease	C4DC/C5OH low C0 and C2	1	0.026
Total		527	

Table 5 distribution of the clinical condition detected during expanded newborn screening according to newborn age at screening.

Table 5. Distribution of the clinical condition detected during expanded newborn screening according to newborn age at screening.

Clinical condition	Age at screening				total
	Age > 7 days	%	Age ≤ 7 days	%	
G6PD Deficiency	178	68.5	82	31.5	260
Cystic Fibrosis	53	67.9	25	32.1	78
Congenital Adrenal Hyperplasia	23	46.0	27	54.0	50
PKU	32	86.5	5	13.5	37
Biotinidase Deficiency	15	50.0	15	50.0	30
Hypothyroidism	4	33.3	8	66.7	12
MSUD	8	72.7	3	27.3	11
Other clinical condition	35	71.4	14	28.6	49
Total	348	66	179	34	527

DISCUSSION

The total number of screened newborns from June 2018 to November 2021 was 3872, the majority are from Duhok city followed by Baghdad city and the number of clinical conditions detected by the expanded newborn screen panel was 527 newborns. The low number of screened newborns when compared to the annual birth rate in the Iraqi population which is about 1258028, 1231697, and 1205236 in 2018, 2019, and 2020, respectively (16) with relatively high clinical conditions detected can be explained by the fact that the clinician, usually, only send the symptomatic newborns or highly suspicious cases.

A comprehensive system that encompasses "education, screening, short-term follow-up, diagnosis, treatment/management, and long-term follow-up/evaluation" underlies the operation of "Newborn Dried Blood Spot Screening (NDBS)" initiatives (17). Economic, political, and cultural factors frequently pose problems for the NDBS system. For a variety of reasons, along with a lack of understanding by the individual as well as the benefits to family, society, and finances, the implementation of NBS in emerging health systems, such as several in the "Middle East and North Africa (MENA) and Asia Pacific (AP)", has been gradual. Nevertheless, most emerging healthcare systems have additional challenges because of the economy, government stability, culture/religion, location, and health/political agendas. All nations with NDBS have had or will face difficulties adopting NBS (18-22).

The NDBS system must be integrated into an operational public health system and be appropriately funded to become effective. Via their national public health insurance schemes, several nations have been able to secure funding, but the procedure is frequently cumbersome and slow. As a result, various finance plans, such as a charging system, ought to be taken into account. A strategy where maternity facilities buy screening kits (collection cards) and are in charge of arranging their compensation is advocated by several appropriate terms. In these situations, caution should be exercised to keep the management and gathering fees that may be added to the patient's test expense to a minimum; alternatively, the consumer fees will grow enormous and be detrimental. All program expenditures, both in the laboratory and nonlaboratory testing components (such as strategy implementation, apparatus, teaching, public relations, follow-up, and specimen storage), must be taken into account when determining fees (23, 24).

The majority of the cases were G6PD deficiency (6.7% of neonates examined), which is common in many Eastern Mediterranean nations, including Iraq (25-27). The incidence of G6PD deficiency in central and southern Iraq has been the subject of some investigations (28-30). Due to the COVID-19 outbreak, there were more infants examined in 2021 than there were in 2019 and 2020.

Even though the Newborn Screening Program, a national program for early identification of two assigned "inborn metabolic disorders, phenylketonuria (PKU), galactosemia (GAL), and congenital hypothyroidism (CHT)",

was launched in April 2013 in Baghdad and Karbala as starting provinces, the program is only available locally, and there has been no progress in expanding the panel by adding other recommended clinical conditions to the program (31).

Successful NDBS have historically resulted from the efforts of a person or group of people engaged in enhancing the health outcomes for infants and their families. Only a few instances—usually in tiny nations like Singapore and Hong Kong—have seen the NDBS program evolve into a form of government assistance. Initiatives at universities and hospitals, however, are now more widespread. Without the health ministry acknowledging the significance of NDBS, these programs have frequently been isolated and have made little progress. Their institutionalization on a national scale typically requires a connection to governmental public health programs. It can take years for these endeavors to develop into a complete system that can effectively serve all babies. Success in the development and institutionalization of NDBS has frequently been attributed to the commitment of committed leaders who work to acquire the necessary knowledge in NDBS medical and laboratory science and whose tenacity results in overcoming political, cultural, and economic obstacles (32).

Among 527 detected newborns during screening, only 34% were tested within the first week of age. Early Phenylketonuria (PKU) diagnosis and treatment are vital to prevent irreversible damage such as neurological impairment and intellectual disability (33). Largely, PKU and other metabolic disorders have not been systematically evaluated and reported in Iraq including KRG (Kurdistan Region; Northern Iraq). Because of that, metabolic disorders, including PKU, have possibly been underestimated (34).

Conclusions

The Duhok project of expanded newborn screening in Iraq, which currently includes 72 tests, will be one of the most comprehensive NBS panels in the world. Most of the detected clinical conditions were not sent at recommended time for newborn screening. NBS has not yet become prevalent in Iraq, thus the screening for metabolic disorders is not normally requested until a patient is already experiencing symptoms.

Recommendations

Public education about the importance of screening is important via coordination between private and public sectors to provide the most up-to-date, comprehensive, and relevant test menu as per the prevalent disorders found within each society. These should run over side by side via physicians, general practitioners, healthcare providers, parents or guardians or any other child family members. An educational campaign using multimedia (radio, television, and newspaper..etc) will encourage and accelerate community learning about NDBS in developing health systems.

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Conflict of interest

The authors declare no conflict of interest concerned in the present study.

Adherence to Ethical Standards

The study was approved by the Research Ethics Committee/Duhok Directorate General Health (Refrence Number 18052022-3-5; date 18 May 2022).

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