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Mini-Review

A Review on the Role of Clinical Chemistry in the Screening for Genetic Diseases in Paediatrics

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ABSTRACT

Background: Genetic diseases are rare single-gene Mendelian conditions, both congenital and hereditary, often causing severe disability and death early. Newborn screening is a population-based screening strategy for identifying neonates with metabolic, endocrine, and other problems for which early detection and treatment can avert severe consequences and symptoms. It is recognized as one of the most successful public health programs. The diagnosis of inherited genetic diseases requires specific biochemical and genetic tests, such as amino acid analysis, organic acid analysis, enzyme assay, and DNA analysis. The study aimed to review the role of clinical chemistry in screening genetic diseases in paediatrics supported by published data or derived from expert consensus.

Review: We searched for scientific websites like Medline, PubMed, Scopus, African Journals Online, Google Scholar and reference books. A systematic review of available literature on the role of clinical chemistry in newborn screening and managing inherited genetic diseases in paediatrics was done.

Conclusion: Therefore, the role of the clinical chemistry laboratory in the screening and diagnosis of genetic diseases is crucial, as it entails performing the correct test on the most appropriate sample type and correctly interpreting the test result.

Keywords: Genetic disease; Newborn screening; Inborn error of metabolism; Genetic testing; Clinical chemistry

INTRODUCTION

A newborn screening program is an essential public health function provided to all newborns [1]. Approximately one-quarter of paediatric hospital admissions in the USA are due to genetic diseases. A large subset of which are a class of metabolic disorders known as inborn errors of metabolism (IEMs) [2]. The occurrence of IEM varies between 1 in 100 and 1 in 200,000, depending on the disorder and the population involved [3]. Inborn errors of metabolism are inherited conditions caused by mutations that affect protein function. Most IEMs are monogenic, with mutant proteins primarily enzymes, but others involve structural proteins, receptors, hormones, or transport proteins [4]. Inborn errors of metabolism (IEMs) commonly manifest in early childhood, although they can also manifest in late childhood or adulthood [2-5]. Some inborn errors of metabolism are usually harmless, while others, if not detected and treated early, can have irreversible clinical implications or result in death.

In some cases, even if no effective treatment is available, it is critical to make a diagnosis [3]. Screening many newborns to discover abnormalities early and avert complications is technically and economically feasible [6]. The majority of the signs and symptoms of IEMs are caused by toxic metabolite buildup or metabolite shortages that are necessary for energy production [2]. Newborn screening can detect many metabolic disorders, allowing early initiation of treatment to prevent morbidity and mortality [5-7]. Many countries have instituted programs for screening all newborn infants for certain genetic metabolic disorders or congenital defects [3,8]. The diagnosis requires specific biochemical and genetic tests such as amino acid analysis, organic acid analysis, enzyme assay, and DNA analysis [2,5]. The role of the clinical chemistry laboratory in the diagnosis of IEMs is crucial, as it entails performing the correct test on the most appropriate sample type and correctly interpreting the test result [2].

LITERATURE REVIEW

Genetics

An individual's inherited characteristics are determined by approximately 50,000 pairs, arranged on 23 chromosomes, each from the father and the mother. These genetic variants may be incompatible with life at one extreme, or they may

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produce biochemical differences detectable only with specialized techniques. Many variations exist between the two extremes, resulting in functional abnormalities [3]. Genetic diseases refer to rare single-gene Mendelian conditions, both genetic and hereditary, often causing severe disability and death early [9]. Mutations in genes that code for specific enzymes or transporters involved in metabolic pathways are the molecular basis of hereditary diseases [4]. As a result, intermediate metabolites accumulate and cannot be metabolized further, or there is decreased formation of essential products [5]. Although the inheritance patterns differ, most of these diseases are autosomal recessive [3,4]. Inherited metabolic disorders are Mendelian disorders or single-gene disorders caused by mutations in a single gene and can be classified based on their hereditary patterns as:

1. Autosomal dominant

2. Autosomal recessive

3. X-linked dominant

4. X-linked recessive [10]

Newborn screening

Screening is a health service in which members of a specified population who do not necessarily perceive themselves to be at risk of a disease or its complications are asked a question or offered a test with the aim of identifying those individuals who are more likely to be helped than harmed by further tests or treatments [9]. Newborn screening is a population-based screening strategy for identifying neonates with metabolic, endocrine, and other problems for which early detection and treatment can avert severe consequences and symptoms [2,7,10]. It is recognised as one of the most successful public health programs [2]. Newborn screening was initially instituted in the 1960s when Robert Guthrie and his colleagues developed a screening assay known as the Guthrie test for screening phenylketonuria by detecting phenylalanine concentration in a dried blood spot on filter paper obtained from the blood of newborn babies. [2,7,11-13]. In industrialized countries, screening programs have been widely adopted [11].

However, most developing countries, especially in Africa, are still lagging. Although a study done in Nigeria shows that there is good acceptability of newborn screening [86.1%] across most groups studied [14]. Nigeria's effort to establish universal newborn screening failed because the logistics of sample movement for newborn screening were not matched with funds. Also, trained staff from zonal centers did not take ownership of the program by including equipment maintenance costs and consumables in their recurrent expenditure [14]. The newborn screening system is comprehensive, encompassing screening and diagnosis and long-term follow-up through the medical home. All of the disorders discovered by newborn screening are chronic, requiring medical treatment and other related services for the rest of the person's life [1].

Characteristics of a screening program

1. The disease should not be clinically apparent at the screening time and should have a relatively high incidence in the population screened.

2. The disease should be treatable, or early treatment should improve the outcome.

3. It must be possible to obtain the screening test result before irreversible damage is likely to have occurred.

4. The screening test should be reliable and straightforward, and the cost of the program should, ideally, be cost savings resulting from early treatment. For example, such treatment may sometimes eliminate the need for prolonged institutional care [2,3,15].

Criteria for newborn screening programs

The criteria are based on the Wilson and Jungner principles developed for the World Health Organization in 1968 [2,13,15].

A. The disease to be screened must:

- Be serious,
- Be fairly common,
- Have a natural history that is understood, and
- Have helpful treatment or genetic counseling.

B. The test used to screen for it must be:

- Acceptable to the public,
- Reliable,
- Valid, and
- Affordable

C. Genetic screening programs require coordination among the testing, the clinical services, and the program management levels to enable the overall objectives of the program to be achieved [9]. This involves the following:

- Organizations of public health,
- Screening and diagnostic laboratories (including clinical chemistry),
- Physicians (chemical pathologists, paediatricians, geneticists, GPs, etc.)
- Families of affected children.

Steps to be followed in a newborn screening program

The different steps that need to be coordinated and tracked in a newborn screening program are [8,11].

- Screening (sample collection and delivery, laboratory testing)
- Follow-up (complete demographic information, satisfactory specimens, abnormal screening results)
- Diagnosis (confirmatory tests, clinical consultation)
- Clinical management (medical home, specialist physician, genetic counselor, dietitian)
- Education (healthcare professionals, parents)
- Quality assurance: analytical (proficiency testing, quality controls, standards), the efficiency of follow-up system, efficacy of treatment, long-term outcome (Table 1).

Table 1: Conditions included in newborn screening program in USA.

	Core conditions	Secondary conditions
Organic acid disorders	Propionic acidemia	Malonic acidemia
	Methylmalonic aciduria	Isobutyrylglycinuria
	Isovaleric acidemia	2-Methylbutyrylglycinuria
	3-Methylcrotonyl-CoA carboxylase	3-Methylglutaconic aciduria
	deficiency	2-Methyl 3 hydroxybutyric aciduria
	HMG-CoA lyase deficiency	
	Holocarboxylase synthase deficiency	
	ß-Ketothiolase deficiency	
	Glutaric aciduria type I	
Fatty acid oxidation disorders	Carnitine uptake defect/carnitine transport defect	Short-chain acyl-CoA dehydrogenase Deficiency
	Medium-chain acyl-CoA dehydrogenase Deficiency	Medium/short-chain L-3-hydroxy acyl-CoA
	Very long-chain acyl-CoA	dehydrogenase deficiency
	dehydrogenase deficiency	Glutaric acidemia type II
	Long-chain L-3 hydroxy acyl-CoA dehydrogenase deficiency	Medium-chain ketoacyl-CoA thiolase deficiency
	Trifunctional protein deficiency	2,4-Dienoyl-CoA reductase deficiency
		Carnitine palmitoyltransferase type I deficiency
		Carnitine palmitoyltransferase type II deficiency
Amino acid/urea cycle disorders		Carnitine acylcarnitine translocase deficiency
	Argininosuccinic aciduria	Argininemia
	Citrullinemia type I	Citrullinemia type II
	Maple syrup urine disease	Hypermethioninemia
	Homocystinuria	Benign hyperphenylalaninemia
	Classic phenylketonuria	Biopterin defect in cofactor biosynthesis
	Tyrosinemia type I	Biopterin defect in cofactor regeneration
		Tyrosinemia type II
		Tyrosinemia type III
Other IEMs	Biotinidase deficiency	Galactoepimerase deficiency
	Classic galactosemia	Galactokinase deficiency
	Glycogen storage disease	
	Pompe disease	
	Mucopolysaccharidosis type 1	
	X-linked adrenoleukodystrophy	

Laboratory testing for newborn screening

Because of technological advances, many IEMs are now included in newborn screening programs. The specimen used has; plasma, urine, Cerebral Spinal Fluid (CSF), dried blood spots, and postmortem specimens. The choice of technique depends on the application or clinical indication. Laboratory evaluation of the IEMs includes routine and specialized testing [2].

1. Routine testing includes the measurement of glucose, electrolytes, ammonia, lactate, pyruvate, renal function tests, liver function tests, urinalysis, and basic hematology tests.

2. Specialized testing used in newborn screening programs is geared toward:

- Direct measurement or detection of metabolites- ELISA, fluorimetric, HPLC, Tandem Mass Spectrometry (MS/MS), LC-MS/MS. Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) is commonly used for the targeted analysis of small molecules, including amino acids, acylcarnitines, and organic acids.
- Measurement of enzyme activity- Spectrophotometry, Fluoroimmunoassay

3. Genetic Molecular studies:

- Polymerase Chain Reaction (PCR)
- Southern blotting
- Allele-specific probe hybridization
- DNA sequencing (Sanger method)
- Real-time PCR
- Nucleic acid microarrays
- Multiplex Ligation-dependent Probe Amplification (MLPA)
- Mass spectrometry
- Massively parallel (next-generation)
- Next-Generation Sequencing (NGS)
- RNA sequencing

Molecular genetics methods are currently used primarily as a backup for confirmation of positive results obtained using less expensive and more comprehensive biochemical or enzymatic

methods, but as molecular methods become more cost-effective, high-throughput, and comprehensive, this situation may change. Beyond the simple diagnosis obtained by biochemical approaches, determining the actual mutations in the affected gene can provide further information about probable severity and medication response. Furthermore, as Next-Generation Sequencing (NGS) becomes more affordable, it is not unreasonable to believe that all babies will be subjected to a full-genome study at some point in the future [16].

DISCUSSION

Many screening tests used in evaluating metabolic disease use similar types of equipment available in clinical chemistry laboratories. What differentiate metabolic testing from routine testing in the laboratory are the compounds analyzed and their correlation to inborn errors of metabolism [2]. Metabolic abnormalities seen in various IEMs are not familiar to physicians requesting metabolic testing, and for this reason, most metabolic tests require an interpretation in addition to any quantitative results. Test reports should include the result, a differential diagnosis based on the abnormal and normal findings, and recommendations for further testing [2]. The report should include information about any testing needed and contact information for the person who wrote it in case questions arise. The results are interpreted correctly when clinical and relevant laboratory information is included with the test requisition. When the results point to various IEMs, it's essential to compare them to the patient's clinical and laboratory data to reduce the differential diagnosis and recommend the best follow-up tests [2,12].

CONCLUSION

Scientific papers and relevant references are examined to evaluate the test's procedures and clinical utility. The laboratory defines the patient populations that the test would be used on, and also, the best test methods for the disease or analyte under investigation are chosen. It establishes or confirms the test performance specifications and the test's quality control parameters. The clinical chemistry laboratory plays a vital role in screening and diagnosing paediatric genetic conditions, which requires performing the correct test on the most appropriate sample type and correctly interpreting test results. Specific biochemical, enzyme activity and genetic tests are needed to confirm the diagnosis.

CONFLICT OF INTEREST

None

REFERENCES

1. Kemper AR, Boyle CA, Aceves J, Dougherty D, Figge J, Fisch JL, et al. Long-term follow-up after diagnosis resulting from newborn screening: statement of the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. Genet Med. 2008;10(4):259-61.
2. Clarke W, Marzinke M . Contemporary practice in clinical chemistry. Academic Press; 2020.
3. Crook M. Clinical biochemistry and metabolic medicine. CRC Press; 2013.
4. Marshall WJ, Lapsley M, Day A, Ayling R. Clinical biochemistry E-book: Metabolic and clinical aspects. Elsevier sci.; 2014.
5. Rifai N. Tietz textbook of clinical chemistry and molecular diagnostics-e-book. Elsevier sci.; 2017.
6. Kenner C, Moran M. Newborn screening and genetic testing. J Midwifery Wom Heal. 2005;50(3):219-26.
7. Comeau AM, Larson C, Eaton RB. Integration of new genetic diseases into statewide newborn screening: New England experience. Am J Med Genet C Semin Med Genet.2004:35-41.
8. Stewart MJ, Shepherd J, Gaw A, Murphy M, Cowan RA, O'Reilly DS. Clinical Biochemistry E-Book: An Illustrated Colour Text. Elsevier sci.; 2011.
9. Andermann A, Blancquaert I. Genetic screening: A primer for primary care. Canadian Family Physician.2010 ;56(4):333-9.
10. Huang S, Xu Y, Liu X, Zhou M, Wu X, Jia Y. Molecular newborn screening of four genetic diseases in Guizhou Province of South China. Gene. 2016;591(1):119-22.
11. Brendan Lee MD, Scaglia. Inborn errors of metabolism: From neonatal screening to metabolic pathways. Oxford University Press; 2014.
12. Centers for Disease Control and Prevention (CDC. Good laboratory practices for biochemical genetic testing and newborn screening for inherited metabolic disorders. MMWR. Recomm Rep. 2012;61(RR-2):1-44.
13. Burtis CA, Bruns DE. Tietz fundamentals of clinical chemistry and molecular diagnostics-e-book. Elsevier sci.; 2014.
14. Nnodu OE, Adegoke SA, Ezenwosu OU, Emodi II, Ugwu NI, Ohiaeri CN, et al. A Multi-centre Survey of Acceptability of Newborn Screening for Sickle Cell Disease in Nigeria. Cureus. 2018;10(3).
15. Sagi M. Ethical aspects of genetic screening in Israel. Sci. Context. 1998;11(3-4):419-29.
16. McPherson RA, Pincus MR. Henry's clinical diagnosis and management by laboratory methods E-book. Elsevier sci.; 2022.