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Review Article

Newborn Screening for Congenital Hypothyroidism and Congenital Adrenal Hyperplasia in Egypt

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Abstract

Newborn screening (NBS) is considered one of the most successful public health programs in the Egypt. It helps identification conditions in asymptomatic newborns at birth, which are known to cause severe morbidity and mortality, with timely treatment prior to disease presentation, thus preventing poor long-term outcomes. Two disorders, congenital adrenal hyperplasia (CAH) and congenital hypothyroidism (CH), when untreated, can lead to devastating, irreversible and fatal outcomes. Permanent cognitive impairment, growth failure and dysmorphic features are seen in congenital hypothyroidism (CH) and early infant death in males with salt loosing CAH (as most females are discovered by presence of atypical genitalia, while males appeared normal). Newborn screening (NBS) for congenital hypothyroidism (CH) was more rapidly adopted throughout Egypt, while NBS for congenital adrenal hyperplasia (CAH) was recently added. Early treatment of CAH is much simpler with taking a pill a day unlike CAH requiring multiple medication doses, and possibly surgery apart from enteral and parenteral stress doses during adrenal crisis. Early newborn screening specifically for those two disorders has a great importance for early diagnosis, early intervention and prevention of catastrophic outcomes.

Key words: Newborn screening (NBS); congenital hypothyroidism (CH); congenital adrenal hyperplasia (CAH)

Introduction

Newborn screening (NBS) is considered one of the most successful public health programs in the Egypt. NBS helps identify conditions in asymptomatic newborns at birth, which are known to cause severe morbidity and mortality, with timely treatment prior to disease presentation, thus preventing poor long-term outcomes. Most of disorders are screened on dried blood spot testing. Moreover, advances in testing methodology have helped ensure high sensitivity and specificity in detection and confirmation of a positive screen. [1]

Screening for a disease should satisfy Frankenburg's three criteria: the disease should be important, prevalent and amenable to prompt treatment. Congenital hypothyroidism (CH) and congenital adrenal hyperplasia (CAH) satisfied all three Frankenburg criteria. [1, 2]

Untreated, each of these disorders has potentially irreversible effects, e.g., permanent cognitive impairment, growth failure and dysmorphic appearance in congenital hypothyroidism (CH), when treatment was too late, as well as early infant death in males with salt wasting CAH. [2]

Although most females were thought to be discovered by the presence of what is now called atypical genital appearance, NBS has identified cases in females, when clinically not suspected. [3]

Congenital Hypothyroidism

The outcomes varied; early replacement therapy spared IQ with scores ranging 64–107 when treated before 3 months, 35–96 when treated between 3 and 6 months and 25–80 when treated after 6 months [4], with similar early detection results and supporting the need for worldwide CH screening [5].

Newborn Screening for Congenital Hypothyroidism: false positive tests must be expected and effectively addressed in order to minimize false negatives, and to avoid unnecessary negative psychological effects on parents. [6-10]

While initial assay for T4 with reflex to TSH has low recall for false positives, initial T4 alone is no longer used. [11-14] Initial screening with TSH will not identify central CH due to TRH (Thyrotropin-Releasing Hormone) or TSH deficiency. [15]

Among advances in treating CH are more rapid normalization of thyroid status with an increase in initial thyroxine dose from 8–10 mcg/kg to 10–15 mcg/kg [16,17] and the ability to identify infants with the rare genetically inherited forms earlier.

False-negative results may be due to prematurity or twin-to-twin transfusion with the CH in the recipient twin obscured by the T4 of the donor twin [18,19].

With application of lower TSH cutoff levels, more infants are identified who may have less severe forms of CH; as many as 50% of these infants may not need permanent treatment [20-22].

To screen with lab testing during pregnancy to minimize the risk of profoundly hypothyroid babies born with CH .the American College of Obstetrics and Gynecology suggested detailed history and physical assessment to identify at-risk pregnancies rather than routine laboratory screenings. [23].

Egypt is one of the countries with low iodinated salt intake and a substantial number of neonates suffering from iodine insufficiency, according to UNICEF [3].

The Egyptian Ministry of Health and Population (MOHP) has approved the use of the TSH assay method to screen for congenital hypothyroidism (CH) [4].

For the years 2007, 2008, and 2009, the program's coverage rates were 92.4 percent, 91.7 percent, and 90.9 percent, respectively. [4]

Etiology

Most cases of congenital hypothyroidism are due to defects of thyroid gland development (dysgenesis) during embryogenesis (sporadic primary hypothyroidism). Dysgenesis, which includes agenesis, hypoplasia and ectopy,

is the most common cause of congenital hypothyroidism. Dysgenesis usually occurs sporadically, with 2–5% of cases being attributable to identifiable genetic mutations. [24-27].

The thyroid hormone stimulating receptor (THSR) and the transcription factors PAX8, NKX2-1 and FOXE1 are expressed in the developing thyroid [26].

Normal thyroid gland formation can be disrupted by defect in expression of any of these genes.

Also, there can be associated additional syndromic features, such as interstitial lung disease, chorea (NKX2-1), renal abnormalities (PAX8), cleft palate, bifid epiglottis, choanal atresia and spiky hair (FOXE1). [25-29]

Although dysgenesis is the most important cause, the incidence of dyshormogenesis is increasing. Dyshormogenesis is due to autosomal recessive genetic defects in thyroid hormone synthesis. [24-26]

Central hypothyroidism caused by dysfunction of hypothalamic or pituitary control of thyroid axis leading to inadequate production of TSH is rare. [27,28]

Management

The key management of CH positive screen includes:

- Confirming diagnosis with serum TSH and free T4 levels, prompt treatment initiation with thyroxine 10–15 mcg/kg and post treatment repeat serum free T4 and TSH at follow-up in two weeks. [20-22]
- Imaging should be done to differentiate the type of dysgenesis using either technetium 99 or iodine 123 scans or ultrasound. Thyroxine tablets can be crushed between two spoons in a small amount of water/formula/breast milk, but is not advisable to mix in a feeding bottle or give with multivitamin as absorption is altered with iron and Vitamin C. [29,30]
- Monthly follow-up with TSH and T4 levels as and when indicated can help. [31-33]

Congenital Adrenal Hyperplasia (CAH)

There are multiple causes of CAH including defects in: 21-steroid hydroxylation, 11 steroid-hydroxylation, 17 alpha hydroxylation-20–22 lyase action and 3 beta hydroxy steroid dehydrogenase. [29]

As CAH from 21-hydoxylase deficiency comprises 90–95% of all cases, causes early fatality, can be easily detected and is treatable, it met the screening criteria to include it in NBS. [33-36]

CAH newborn screening

Newborn screening improved overall case detection of congenital adrenal hyperplasia worldwide. The screening also improved detection of the salt wasting form, which had previously been missed in some male infants, resulting in deaths. [36]

In Egypt, This prevalence (1 in 1209) is much higher than the worldwide incidence (1 in 14 199) live births [7]. However, it lies between the highest two incidences reported; the Yupik Eskimos of Western Alaska (1: 282) [2] and that of Rio de Janeiro, Brazil (1: 2009) [21].

Beside the high frequency, the cost for screening was very low (US$ 6, 36 per screened infant) which makes the screening cost–benefit relationship very effective. [21]

Etiology & Genetics

CAH comprises a group of autosomal recessive disorders, caused by mutations in genes encoding enzymes in pathways involved in cortisol biosynthesis: 21-hydroxylase, 11 beta-hydroxylase, 17 alpha-hydroxylase 20–22 lyase, 3 beta-hydroxy steroid dehydrogenase, steroidogenic acute regulatory protein (StAR) and cytochrome P450 oxidoreductase. [34]

CAH clinical presentation depends on which of the above are deficient, causing alterations in glucocorticoid, mineralocorticoid and sex steroid production, which lead to disordered physiology and anatomy.[35]

More than 95% cases of CAH are due to 21-OH deficiency, characterized by impaired cortisol and aldosterone production and androgen excess. [36]

There are three phenotypes of CAH due to 21-OH deficiency: classic salt losing, classic non-salt losing and non-classic (previously termed late onset).

Screening programs target 21-hydroxylase deficiency as it is the most prevalent with the salt wasting form being the most devastating form if missed. [35]

The key management of CAH positive screen includes: Confirming diagnosis with serum electrolytes and 17-OHP levels and consultation with pediatric endocrinologist, and subsequent ACTH stimulation testing in some cases, prompt treatment with cortisol (10–15 mg/m^2/day divided in three doses) and mineralocorticoid (fludrocortisone 0.05–0.1mg/day) and salt supplementation, and education of family on how to administer medication and adrenal crisis management with stress dose of oral steroids during stress/intercurrent illnesses or IM glucocorticoid if any oral intolerance. [39]

- Evaluation of internal genital anatomy by ultrasound in presumed females.
- Consultation with surgical specialists with expertise in disorders of sexual differentiation to help with family's decision making.
- Follow-up with pediatric endocrinology in two weeks, one month, and every three months when stable.
- Use of prenatal dexamethasone therapy to mitigate or prevent virilization of external genitalia in females with CAH. While this has shown some efficacy in clinical trials, risk to unaffected fetuses continues to raise ethical concerns.[40]

Summary and conclusions

Newborn screening (NBS) is considered one of the most successful public health programs in the Egypt.

There have been significant advances in the diagnosis and treatment in patients

with congenital hypothyroidism. CH screening has been a successful public health program, where it has been implemented. In the seventy years since the initial reports of successful treatment of CAH, advances in knowledge of the underlying biochemistry and genetics have allowed for substantial improvements in medical, psychological and surgical treatment.

Abbreviations

CAH: Congenital adrenal hyperplasia

CH: Congenital hypothyroidism

THSR: Thyroid hormone stimulating receptor (THSR)

TRH: Thyrotropin-Releasing Hormone)

NBS: Newborn screening

Conflict of interest

The author has no conflict of interests to declare.

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