

Congenital hypothyroidism and neonatal screening in Saudi Arabia.

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Abstract

Congenital hypothyroidism (CH) represents one of the most common preventable causes of mental retardation. Neonatal screening programs for CH have almost eliminated the problem of severe mental retardation previously observed in infants who were not diagnosed and treated early in infancy. Screening either utilizes cord blood or an elute of whole blood collected on filter paper by heel prick on day 5-7 of life. Screening based on either the primary determination of serum thyroid screening stimulating hormones senthyroxine or determination of (T4) with back-up of TSH determination for infants with the lowest (10%) of T4 levels has been used. In Saudi Arabia, the programs utilize cord TSH determination. Of 1,007350 newborns screened, 306 infants were diagnosed to have CH, indicating an incidence of 1:3292. A regional variation in the incidence was observed. Of all infants with CH who were adequately studied, 147 infants, the gland was found to be aplastic in 32 (21.8%), while in 62 (42.2%) the gland was ectopic. Thyroid hormone dyshormonogenesis was present in 53 infants (36%). An increased risk of other congenital anomalies was noted. Also, a transient iodine organification defects in infant with ectopic thyroid gland was reported.

Keyword: Congenital, hypothyroidism, Saudi Arabia, screening

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Introduction

Congenital hypothyroidism (CH) represents one of the most common preventable causes of mental retardation. Its incidences varied worldwide (1:3500 – 1:5000), with Saudi Arabia being one of the highest (1:2,500) [1-3]. In the past 40 years, neonatal screening programs for CH have almost eliminated the problem of severe mental retardation previously observed in infants who were not diagnosed and treated early in infancy. The neuropsychological evaluation of children with CH detected early has shown normal mental development in most cases, although, a certain percentage of infants albeit treated early, exhibit minor anomalies of mental development. Many studies had shown that the eventual intellectual outcome depends on age at start of treatment, severity of clinical and biochemical hypothyroidism at diagnosis, bone maturation at birth, and optimal therapy [4].

In Saudi Arabia with a rapidly advancing health care system, neonatal screening for metabolic disorders has become a necessity. In light of the results of local studies [1,2,5] which showed a high incidence of CH, the Ministry of Health in collaboration with the College of Medicine of King Saud University established in 1989 an advisory

committee for neonatal screening for metabolic disorders, with the main objective of promoting and establishing regional screening centres and supervising the quality of service provided.

In this review we try to present a comprehensive coverage of congenital hypothyroidism from different angles, i.e. epidemiology, screening results, and diagnosis.

Anatomy and Physiology

The thyroid gland is visible in the three week embryo as an endodermal projection between the first and second bronchial arches, a point marked by the foramen cecum at the base of the tongue. During the subsequent three weeks it migrates to lie in front of the thyroid cartilage. The factors that control its migration are unknown. Originally, it is attached to the foramen cecum by the thyroglossal duct, which usually atrophies. Colloid formation appears by 10 weeks.

The fetal thyroid gland is capable of trapping iodine by 8-10 weeks and producing thyroxine (T4) by 12 weeks of gestation. Production of hypothalamic thyrotropin releasing hormone (TRH), and pituitary thyroid stimulating

hormone (TSH) occur about the same time but integration and function of the hypothalamic-pituitary-thyroid axis with negative feedback does not occur until the second half of pregnancy. Prior to mid-gestation, the fetus appears to be dependent on maternal thyroid hormone for normal development. Recent studies show that approximately one-third of maternal T4 crosses the placenta to the fetus. After birth, there is a surge of TSH which peaks at 30 minutes in the range of 70-100 mU/L, resulting in increased serum T4 and T3 levels which gradually fall down over the first four weeks of life. In the premature infant, however, serum T4 levels are lower, but rise to meet full term infant levels by approximately six weeks.

Essentially, all the steps involved in thyroid hormone synthesis including iodine trapping, oxidation, organification, coupling and secretion are under control of TSH. The majority of T4 and T3 are carried in the circulation by binding proteins, hence, TBG deficiency or excess will affect measurements of total hormones concentration. Measurements of free hormone levels, therefore, are more accurate.

Absent or mal-descent of the thyroid gland or an inborn error of thyroid hormone synthesis leads to congenital hypothyroidism. Because the vast majority of infants do not display any manifestation of hypothyroidism at birth. Since in the absence of prompt replacement therapy the developing brain would be damaged. Screening for congenital hypothyroidism was initiated in Quebec, Canada in 1972. Since then, this practice has spread to most of the industrialized world. Racial differences in the incidence of CH was noted [6].

Screening Approaches

Except for very limited programs which utilize cord blood TSH for their screening, serum concentration of TSH and/or T4 are measured from an eluate of whole blood collected on filter paper by heel prick on day 5-7 of life. Screening based on the primary determination of TSH constitutes the most sensitive index for the detection of primary hypothyroidism with recall rates less than 0.05%. However, secondary or primary hypothyroidism with a delayed rise in TSH would be missed. Screening based on primary determination of T4 with backup TSH determinations for infants with the lowest (10%) of T4 levels has also proved to be effective. However, some infants with functioning ectopic thyroid tissue or with mild dys-hormonogenesis can be missed.

Clinical management of neonates with suspected congenital hypothyroidism

Infants with high TSH and low T4 or FT4 have CH until proved otherwise.

Management should include

Confirmation:

The infant should be recalled. A complete history including prenatal thyroid status (drugs and medications) and family history should be obtained, and physical examination should be performed. Serum for confirmatory measurements of TSH and T4 or FT4 concentration should be done. Other investigations such as TBG and anti-thyroid antibodies should be carried out when indicated.

Diagnostic Nuclear Medicine Studies

Thyroid scan using Tc-99m pertechnetate (Fig. 1) or Iodine-123 with or without Perchlorate Discharge Test (PDT), when indicated, may be undertaken prior to the onset of therapy to determine the underlying etiology. For thyroid scanning, Tc-99m is preferred to Iodine-123 because it is available around the clock, much less expensive, employs shorter scanning time, yields less radiation dose, and better defines the thyroid in relation to the surrounding tissue. The usual dose of Tc-99m pertechnetate in children is 13.5 kBq (500 uCi) administered intravenously and imaging is performed 15 to 20 minutes after that using a gamma camera equipped with a low energy general purpose collimator. An initial zoomed image and another unzoomed image, to show the salivary glands and the stomach, are obtained. Radioactivity in the syringe before and after injecting is measured to give the corrected administered dose to measure thyroid uptake. The normal Tc-99m-uptake in children is in the range between 0.5% and 4.0%.

Iodine-123 thyroid scan is performed by giving 1.35 kBq (50 uCi) orally, imaging the thyroid and measuring the uptake at 6 and 24h.

The PDT is performed using 1.35 kBq (50 uCi) of Iodine-123 instilled directly in the mouth followed of water or milk to wash the mouth. Thyroid uptake is measured using a scintillation probe and scaler at 1 and 2 hours before administering a 400 mg dose of potassium perchlorate to measure the rate of iodine washout every 15 minutes for 1 hour and every 30 minutes for another 1 hour. When organification defect is suspected, PDT test is performed for confirmation (Fig 2). A discharge rate of more than 50% indicates a virtually complete organification defect while a discharge rate between 20% and 50% indicates a partial defect.

If an ectopic thyroid gland is identified, a permanent form of hypothyroidism exists. If the thyroid scan is compatible with aplasia (i.e. no uptake), however, this may not represent agenesis. Infants with hypothyroidism resulting from a TSH receptor or trapping abnormality will appear to have no uptake, as well as infants whose mothers had an autoimmune disorder resulting in the production of thyrotropin receptor blocking antibodies. In this setting,

if an ultrasound examination of the thyroid confirms aplasia, again a permanent form of hypothyroidism has been established. However, if an ultrasound examination shows a normal thyroid gland, further diagnostic studies must be undertaken. If permanent hypothyroidism has not been diagnosed prior to the onset of therapy, it is recommended that treatment be discontinued sometime after the age of 3 years for 30 days to determine permanency of the hypothyroidism [7].

Management

The aim of treatment is to raise the serum T4 concentration as rapidly as possible up to the normal range to reverse any effects of fetal hypothyroidism. The American Academy of Pediatrics recommended an initial starting dose of thyroxine of 10-15 ug/kg/day [8]. A typical full-term baby is therefore started on 50 ug daily. However, a lower dose has been suggested [9-11]. Serum T4 and TSH determinations should be carried out frequently in the first 3 years of life to ensure that serum T4 concentration remains in the upper half of the normal range for age, and that the TSH remains suppressed into the normal range (<5 mU/L). In general, this means determinations 2 to 4 weeks after the initiation of therapy, every 1-2 months in the first year, every 3 months between 1 and 3 years of age, and every 6 months thereafter until growth is completed.

Neonatal Screening for Congenital Hypothyroidism in Saudi Arabia

Program organization

Regional screening programs were established in the different health regions which were equipped and supervised by local regional committees and consisted of a paediatrician, laboratory technician, administrator and social worker. Scientific and technical back-up were made available to all regions through the central committee.

Screening protocol

Considering the obstetric practice in Saudi Arabia where ~95% of mothers deliver in hospitals, but with the majority being discharged within 24h, the program utilizes umbilical cord serum with thyroid stimulating hormone (TSH) so as to achieve the maximum diagnostic benefits. At the time of delivery, 4 ml of cord blood is collected in a sterile tube from the placental side of the cord before delivery of the placenta. Serum is separated immediately and kept at -20C⁰ until the samples are delivered to the Regional Central Laboratory. During transportation samples are kept in insulated containers. TSH is assayed on single specimens using the Delfia Immunofluorescent (Pharmacia Diagnostic, Wallac Oy, Finland). Total thyroxine (T4) or free T4 is measured using Delfia kits (if indicated).

For quality control of TSH and T4 determinations at least three control sera (normal, low and high levels) are analysed in each series. Based on available data in the literature and the results of our pilot study, TSH concentration of more than 60 mU/l are considered suggestive of CH and warrant examination of the infant and repeat testing. Cord serum TSH values of 30-60 mU/L initiate testing cord serum for T4. Those with T4 less than 80 nmol/l are also considered suggestive of CH and warrant recall of the infant. Cord serum TSH below 30 mU/l is considered normal. The quality control of the regional screening programs are done via lyphocheck immunoassay control serum by Biorad, California, USA.

Confirmation and further diagnostic evaluation and follow-up

After notification of a suspected case, the paediatrician will call the family for confirmation (repeat TSH and T4). At the time of diagnosis, clinical data are obtained which include: sex, age, nationality, consanguinity, family history of thyroid disorders, drug or irradiation during pregnancy, and symptoms and signs of hypothyroidism. Thyroid scan, to identify the etiology, was performed when feasible using sodium pertechnetate (Tc 99m). Perchlorate discharge test was performed in patients with suspected dyshormonogenesis following standard procedure. Infants confirmed with CH were treated initially with L-thyroxine 10-15 ug/kg/day, which was adjusted thereafter based on clinical and biochemical findings as recommended.⁽¹³⁻¹⁴⁾

Results and Discussion

Initial analysis of 1,007,350 newborns revealed congenital hypothyroidism in 306 indicating an incidence 1 in 3292 (Table 1). A regional variation in the incidence was observed⁽¹³⁻¹⁴⁾ due to multiple siblings involved in the family, and high consanguinity rate [15]. Of all infants with CH who were adequately studied, 147 infants, the gland was found to be aplastic in 32 (21.8%), while in 62 (42.2%) the gland was ectopic. Thyroid hormone dyshormonogenesis was present in 53 infants (36%) [7].

We have proved the transient nature of iodine organification defects in infants with ectopic thyroid glands.⁽¹⁶⁾ The familial nature of thyroid gland ectopic was also suggested.⁽¹⁷⁾ An increased risk for other associated congenital anomalies was observed [18].

Many of the issues and questions that originally arouse have been resolved. Our protocol showed an acceptable recall rate and proved to be cost-effective. The incidence of CH in our country is higher than that reported from Europe and America [3-13].

Although an empirical initial dosage of 10-15 µg per kg per day of L-thyroxine is adequate and rapid in normalizing the thyroid status of infants with CH detected by neonatal screening, many infants who were started on higher dosages 12.3 -14.7 µg/kg/day, showed elevated levels of FT₄ which could expose infants to a dangerous hyperthyroxinaemia and have a potential to cause premature

synostosis and delayed development, therefore, an initial lower dosage of 10-12 µg/kg/day of L-thyroxine with frequent and close monitoring of doses with FT₄ and TSH levels is more appropriate and safer than the currently recommended dosage of 10-15 µg/kg/day for initial treatment of infants with congenital hypothyroidism [8,12,19].

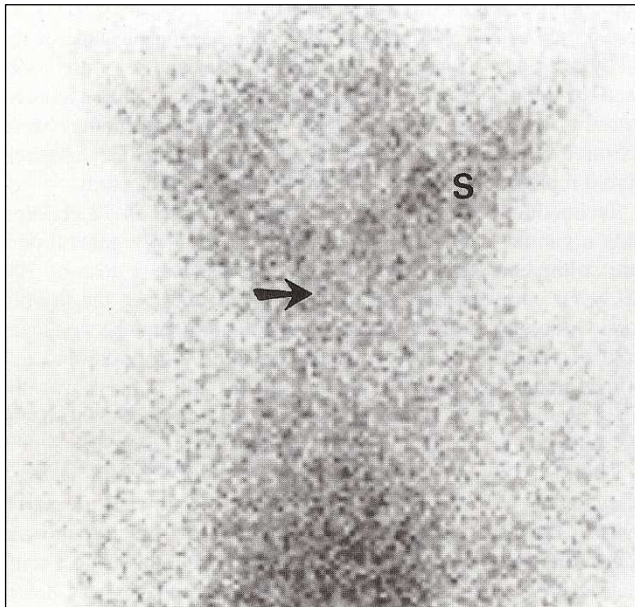


Figure 1a: ^{99m}Tc- pertechnetate thyroid scintigraphy in a newborn with thyroid aplasia. No thyroid tissue is seen in the neck (arrow). Activity is seen in the salivary gland (S).

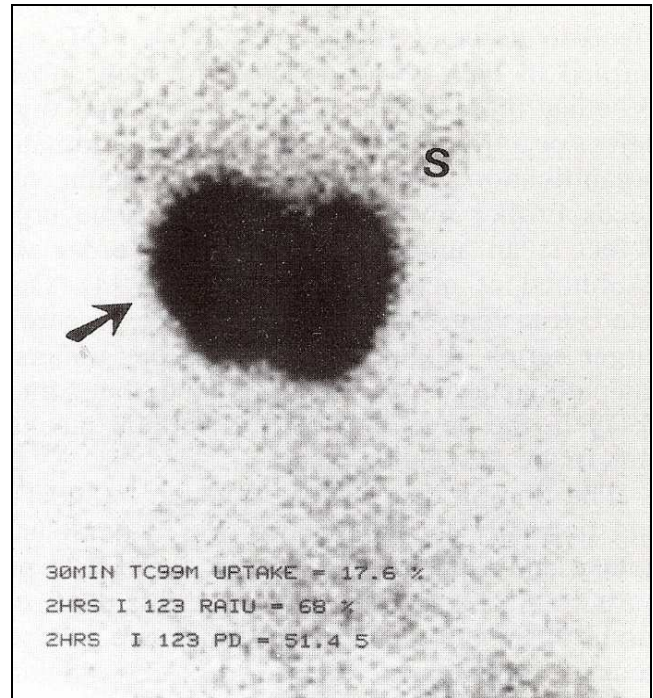


Figure 1c: ^{99m}Tc pertechnetate thyroid scintigraphy revealing a eutopic enlarged gland (arrow), which is demonstrating a marked increase in activity. S, salivary gland

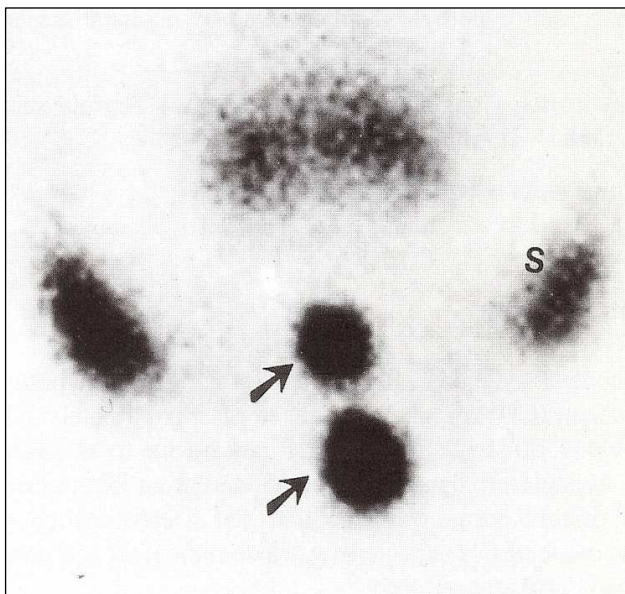


Figure 1b: ^{99m}Tc pertechnetate thyroid scintigraphy. Note the two areas of uptake in an ectopic position (arrows). S, Salivary gland

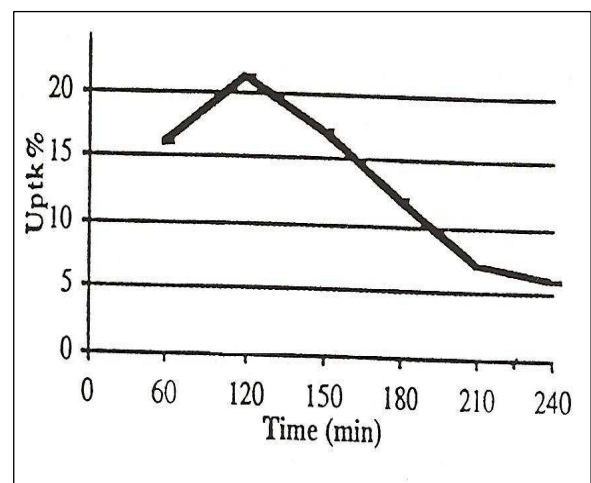


Figure 2: Perchlorate Discharge Test (PDT): Positive test with 2 hrs discharge = 65%.

Table 1. Incidence of confirmed congenital hypothyroidism by the regional screening programs

Region	Total # of newborns creened	No. of confirmed cases*	Incidence
1. Riyadh	283,647	83	1:3417
2. Qassim	75,024	21	1:3573
3. Hail	32,750	5	1:6550
4. Dammam	65,523	20	1:3276
5. Hassa	57,176	21	1:2723
6. Tabuk	31,431	10	1:3143
7. Madina	82,371	28	1:2942
8. Makkah	75,874	25	1:3035
9. Jeddah	40,659	10	1:4066
10. Taif	55,404	20	1:2770
11. Baha	23,128	3	1:7709
12. Assir	65,774	16	1:4110
13. Jizan	38,303	10	1:3830
14. Najran	30,810	22	1:1400
15. Hafer Al Batin	15,977	4	1:3994
16. Qurayat	9,360	2	1:4680
17. Jouf	7,920	1	1:7920
18. Arar	12,095	2	1:6047
19. Bisha	4,124	3	1:1374
TOTAL	1,007,350	306	1:3292

*Figures exclude those infants in whom confirmation was not possible.

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