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Original Research Article.

Congenital Hypothyroidism

Badriah Abdulrahman Alsabah[1*], Ahmed Yaseen Alrefaei[2]

[1*]Medical Intern, Prince Salman Armed Forces Hospital, Tabuk, Saudi Arabia.
[2]Medical Student, Tabuk University, Saudi Arabia.

ABSTRACT

Background: 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.

Methods: 306 infants were diagnosed to have CH, indicating an incidence of 1:3292.

Results and Conclusion: 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.

Key words: Congenital, Hypothyroidism, Neonate.

***Correspondence to:**

Badriah Abdulrahman Alsabah
Medical Intern,
Prince Salman Armed Forces Hospital,
Tabuk, Saudi Arabia.

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INTRODUCTION

Congenital hypothyroidism is one of the most important diseases of the newborn, which may lead to mental and physical retardation when treatment is delayed or an appropriate dosage of thyroxine is not used. The physical findings of hypothyroidism are nonspecific, and typical clinical features are observed in only 5% of the neonatalcases.[1]

Embryology and physiology of the thyroid in the fetus – The thyroid gland originates as a proliferation of endodermal epithelial cells at 3 to 4 weeks of gestation. Synthesis and secretion of thyroxine (T4) and triiodothyronine (T3) starts from 12 weeks of gestation.

Hypothalamic pituitary-thyroid (HPT) axis begins to develop in the first trimester and thyrotropin- releasing hormone (TRH) and thyroid stimulating hormone (TSH) are also detectable by the end of first trimester. However, the activity in the second half of gestation, the T4 and TSH levels increase progressively. In the first trimester, the fetus is dependent on transplacental passage of thyroid hormones.[2]

In the hypothyroid fetus, this transplacental passage of maternal thyroid hormones is critical for neuroprotection throughout the intra-uterine life. The cord blood T4 concentration at birth in infants who are unable to synthesize T4 is 20- 30% of normal. In addition, there is increased conversion of T4 to T3 in the fetal brain by the activity of type 2 deiodinase, resulting in increased local availability of the physiologically more important T3. Near normal cognitive outcome is possible in even the most severely affected infants with CH as long as postnatal therapy is initiated early in optimum doses and maternal thyroid function is normal. In contrast, when both maternal and fetal hypothyroidisms are present as of HPT axis is low with insufficient production of thyroid hormones by the fetus until about 18-20 weeks of gestation. In the second half of gestation, the T4 and TSH levels increase progressively. In the first trimester, the fetus is dependent on transplacental passage of thyroid hormones.[2]

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Similarly, maternal subtle or overt hypothyroidism during pregnancy have also been seen to have an adverse impact on the neuro- intellectual outcome of the offspring.[4]

Newborn screening for congenital hypothyroidism (CH) began in 1970s and the rationale for such screening is well established. Newborn screening for CH is routinely done in developed countries, while in developing countries a routine screening program for CH is not yet universal. Children with CH are being missed at birth and are often diagnosed late in infancy. We did a retrospective analysis of our neonatal screening program for CH using day 4 thyroid stimulating hormone (TSH).[5]

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).[6] 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.[7]

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[8] 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.

CONGENITAL HYPOTHYROIDISM

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 T4crosses 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 T4and T3levels which gradually fall down over the first four weeks of life. In the premature infant, however, serum T4levels 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 T4and T3are 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 wasnoted.[9]

MATERIALS AND METHODS

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 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.[10]

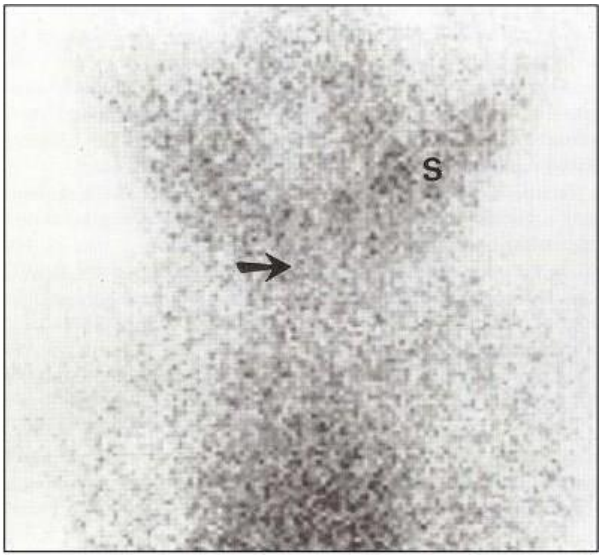

Figure 1a: 99mTc- pertechnetate thyroid scintigraphy in a newborn with thyroid aplasia. No thyroid tissue is seen in the neck (arrow). Activity is seen in the salivary gland (S).

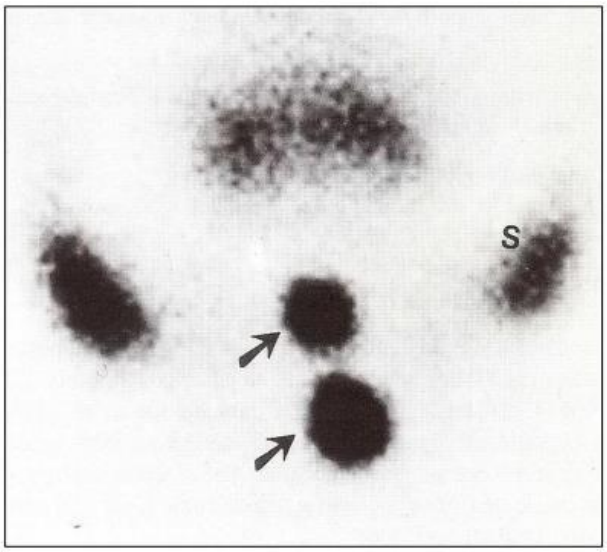

Figure 1b: 99mTc pertechnetate thyroid scintigraphy. Note the two areas of uptake in an ectopic position (arrows). S, Salivary gland

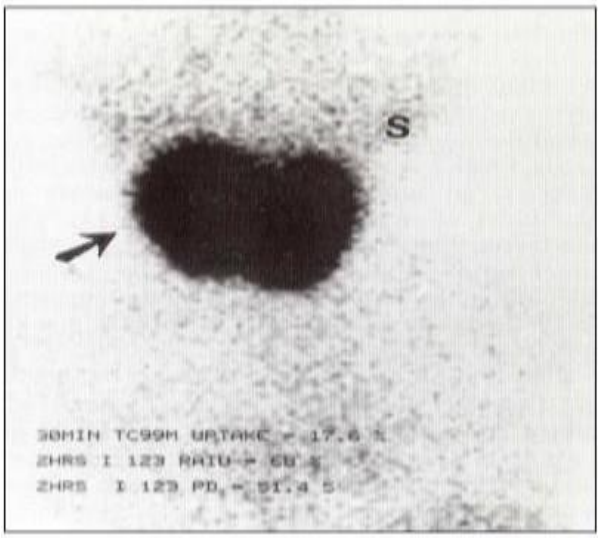

Figure 1c: 99mTc pertechnetate thyroid scintigraphy revealing a eutopic enlarged gland (arrow), which is demonstrating a marked increase in activity. S, salivary gland

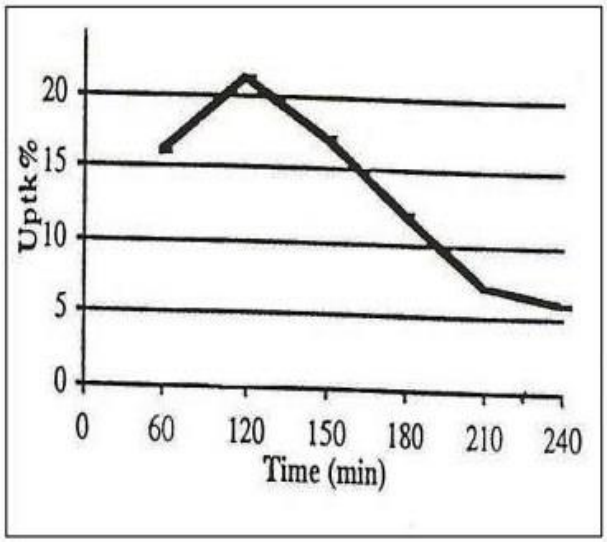

Figure 2: Perchlorate Discharge Test (PDT): Positive test with 2 hrs discharge = 65%.

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.[11] A typical full term baby is therefore started on 50 ug daily. However, a lower dose has been suggested.[12] Serum T4 and TSH determinations should be carried out frequently in the first 3 years of life to ensure that serum T4concentration 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).

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]

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

	Region	Total # of newborns screened	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**

RESULTS AND DISCUSSION

Initial analysis of 1,007350 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.[14] 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%).[15]

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

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.[17]

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 saver than the currently recommended dosage of10-15 µg/kg/day for initial treatment of infants with congenital hypothyroidism.[18]

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