Frequency of Congenital Hypothyroidism (CH) in Neonates of a Tertiary Care Hospital of Karachi, Pakistan

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Abstract

Objective: To determine the frequency of congenital hypothyroidism among healthy newborns presenting to a public health facility in Karachi, Pakistan.

Methods: This cross sectional study was carried out for six months duration at the Well Baby Clinic, Paediatric unit III, Civil hospital Karachi. Neonates of both sex delivered after 37 weeks of gestation, at Civil Hospital Karachi and visited the well baby clinic, after 48 hours of birth to <4 weeks of age for follow up were included in the study. A 3 cc venous blood sample taken for serum Thyroid Stimulating Harmone (TSH) level. Data analysis was done using SPSS statistics version 16.

Results: A total of 215 healthy newborns were included, 112 were male and 103 female patients. Congenital hypothyroidism was considered according to the TSH value. The results showed that 35 patients had TSH >40 (μU/ml).

Conclusion: This study shows that in the screening for the congenital hypothyroidism, 16.3% had a TSH level of >40 (μU/ml). This suggests that screening of hypothyroidism should be mandatory in all newborns especially in our region for early diagnosis and treatment of congenital hypothyroidism.

Keywords: Congenital hypothyroidism, Thyroid Stimulating Hormone (TSH), newborn, Well Baby Clinic

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Introduction

The thyroid is a small, butterfly-shaped gland located below the neck. It secretes thyroid hormones necessary for metabolism and growth, i.e. thyroxine (T4) and triiodothyronine (T3)[1]. Neonates rely on their own endogenous thyroid production that reaches term levels at approximately 18 to 20 weeks gestation[2]. The thyroid gland requires iodine ingested in the diet for the synthesis of thyroxine (T4) and triiodothyronine (T3). Physiologically, T3 is the active hormone in the thyroid and is at least three times stronger than T4 in terms of metabolic potency[3].

Thyroid hormone is critical for many neurodevelopmental events through its regulation of genes that code proteins essential for neurogenesis, neuronal migration, synaptogenesis, and myelination. Animal models of neonatal hypothyroidism demonstrate that thyroid hormone plays a crucial role in these neurodevelopmental events in developing subcortical and cortical posterior regions of the brain, including the cerebellum, striatum, hippocam-

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pus, and corpus callosum[4]. Therefore, insufficient thyroid hormone levels in utero and early life may result in the abnormal development of brain structures essential to cognitive ability.

Thyroid hormones are controlled by thyroid stimulating hormone (TSH) secreted from the anterior pituitary gland in a negative feedback system. Thyroid hormones are responsible for promoting protein synthesis, controlling growth, and influencing carbohydrate, lipid, and vitamin metabolism[4].

Inadequate secretion of thyroid hormone results in lethargy, cognitive impairment, stunted growth, developmental delay, feeding difficulties, constipation, low core temperature, and bradycardia; if it occurs prenatally, it may cause other congenital anomalies[4]. The abnormality in thyroid gland development, such as dysgenesis, agenesis, or hypoplasia, or iodine deficiency leads to congenital hypothyroidism (CH).

Primary congenital hypothyroidism, the most common form of congenital hypothyroidism, occurs as a result of developmental defects of the thyroid gland, known as thyroid agenesis or dysgenesis, or is due to disruptions in thyroid hormone biosynthesis, also known as thyroid dyshormonogenesis[5]. In the majority (80%) of cases, a structural defect of the thyroid gland is present: an ectopic gland in a cranial, sometimes lingual, position; thyroid gland hypoplasia; or the complete absence of thyroid tissue[6]. Congenital hypothyroidism is one of the most common preventable cause of mental retardation. It causes irreversible mental and physical disability if remains undetected and/or untreated. Diagnosis and treatment of CH before 3 months are mandatory to avoid cretinism. CH is defined in accordance with the update of newborn screening in CH in journal of American Academy of Pediatrics (TSH>40 mIU/mL)[7].

Minor variants of thyroid dysgenesis include the absence of the thyroid isthmus or a lack of one-in most cases the left-lobe of the thyroid. This thyroid dysgenesis can be found with a frequency of 1 in 1,000-2,000 individuals without a pre-existing diagnosis of hypothyroidism[8]. These children are affected by a defect of thyroid hormone synthesis, which occurs in most cases as an autosomal recessive trait of inheritance. Secondary congenital hypothyroidism, also termed central congenital hypothyroidism, is caused by deficiencies in TSH, for example, in patients with pituitary insufficiency or structural abnormalities of the pituitary gland or hypothalamus[5].

Newborns suffering from CH have low blood thyroid hormone levels, despite high blood TSH levels. As a result, they have slower metabolisms and brain development is impeded. CH is the most prevalent endocrine disorder in newborns[9], affecting one in 3000-4000[10]. However, the prevalence of CH around the world varies across different population groups. Likewise, the predominant disease aetiology also varies. As newborn screening programs have proliferated, CH prevalence has slowly increased with better methods of case detection and increased disease awareness in screened populations. Globally, the prevalence of CH approaches 1:3000, with substantially higher prevalence in iodine deficient areas, sometimes in excess of 1:900[11].

Racial and ethnic differences in the prevalence of CH vary across populations. Variations in prevalence have also been reported within various populations. In the USA, for example, African-Americans appear to have a CH prevalence about half that of Caucasians, while Hispanics have a rate about 40% higher and Native Americans may have an even higher rate[11]. Recent research has shown that much of this discrepancy may be attributed to differences in thyroid ectopy and are gender related[11].

One study carried out at Shifa hospital Islamabad, found 166 cases with high TSH and 78 cases with low T4 from 949 screened[12]. In another study carried out at PIMS hospital Islamabad, Raza et al[13] found 3 cases of congenital hypothyroidism among 1337 screened bases revealing incidence of hypothyroidism to be one case per 445 newborns. In a study conducted in a tertiary care hospital of Karachi 5000 newborns were screened and five

cases of congenital hypothyroidism were diagnosed. The study revealed incidence of hypothyroidism 1:1000 which is 4 times higher than that in west[14].

The timing of diagnosis is crucial; the later the treatment is started, the worse the neuro developmental outcome and IQ will be. Infants with CH appear to be protected during the first few weeks of life due to the maternal thyroid hormone that crosses the placenta to the fetus[15], the best outcome is when treatment is started by two weeks of age. If treatment is not started, or significantly delayed, clinical features include facial puffiness, large tongue, hoarse cry, hypothermia, hypotonia, skin mottling, prolonged jaundice, poor feeding, constipation, lethargy, large fontanelles, abdominal distention, and umbilical hernia. Though data from Pakistan is available, however, very few studies have been published from our local institutions, where bulk of the patients come also from the rural areas of the country. Hence, we decided to conduct this study with the objective of determining the frequency of congenital hypothyroidism among healthy newborns presenting to our public health facility in Karachi.

Patients and Methods

The Cross Sectional study was conducted in Well Baby Clinic of peadiatric unit III Civil Hospital Karachi (CHK) for a duration of six months from December 2013 to June 2014. All newborn, delivered after 37 weeks of gestation visiting the well baby clinic, Peadiatrics unit-III in CHK aged after 48 hours of birth to <4 weeks of age were included in this study, as serum of babies less than 48 hrs of life contain mother's serum level of TSH. Neonates admitted for reasons like sepsis or congenital anomalies, those already transfused and those with known hypothyroid mothers were excluded from the study.

After counseling and informed consent from parents about the screening test samples were taken. Detailed information including the history and clinical findings were recorded in a predesigned clinical format in order to detect predisposing factors in relation to hypothyroidism. All tests were done free of cost. A 3cc venous blood taken for serum TSH level. After collection of samples, they were sent to Central Lab in CHK, where estimation of TSH was performed.

The TSH level above 40 MIU/L was considered for congenital hypothyroidism in babies. The babies having significant raised TSH level were recalled for advising as per need for consultation.

For the statistical analysis SPSS v.16.0 was used. Quantitative variables e.g. age, weight, head circumfrence, and height were expressed as mean and standard deviation. Frequency of CH and gender were expressed in numbers and percentages. To control the effect modifier data were stratified through gender, age, weight, and height and occipto-frontal circumference of neonate. Post-stratification chi-square test was applied. $p \leq 0.05$ was taken as significant.

Sample size in this study was determined by Open Epi calculator, considering16.8% a high TSH was reported on babies was born at Shifa International Hospital, Islamabad[11] in neonates, on 95% confidence interval and 5% margin of error, the required sample size calculated was 215 neonates. Sampling technique was non-probability consecutive sampling.

Total 215 patients, either gender with age between 48 hours of life to 27th day, visiting the well baby clinic at CHK were included in the study to determine the frequency of congenital hypothyroidism.

Descriptive statistics were calculated. Qualitative variables are presented in frequency and percentages. The quantitative variables are presented in mean and standard deviation. Chi square test is also applied to determine the association of modifiers on outcome with p-value $\leq$ 0.05 being considered as significant.

Results

Among the total number of participants, there were 112 male and 103 female patients. The overall

Table 1. Frequency Distribution of Congenital Hypothyroidism (n=215)

	Frequency (n)	Percentage (%)
POSITIVE	35	16.3%
NEGATIVE	183	83.7%
TOTAL	215	

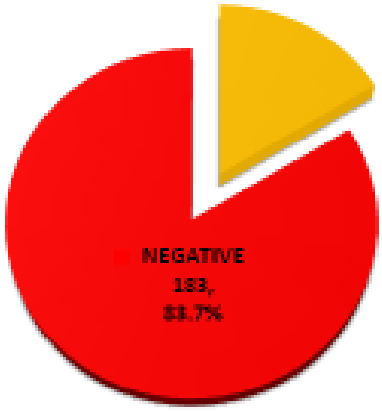

Fig. 1. Frequency distribution of Congenital Hypothyroidism

Table 2. Descriptive statistics of weight, height, occipital-frontal circumference and TSH in congenital hypothyroidism positive patients(n=35)

	Mean	SD	Range	Min	Max
Age (days)	10.31	7.91	23	3	26
Height (cm)	50.82	1.80	7.4	46.7	54.1
Weight (grams)	1564.83	304.52	1534	1002	2536
FOC (cm)	36.97	1.46	5	35	40
TSH (μU/ml)	44.89	3.16	11	41	52

Table 3. Frequency, distribution of height, weight, occipital frontal circumference and TSH (according to stratified groups).

.		Frequency (n)	Percentages %
Height (cm)	< 51	48	22.3%
	> 51	167	77.7%
Weight (Grams)	< 1645	132	61.4%
	> 1645	83	38.6%
FOC (cm)	< 37	122	56.7%
	> 37	93	43.3%
TSH (μU/ml)	< 40	180	83.7%
	> 40	35	16.3%

mean age was 14 days, 14 ± 7.10 days, with range of 24 (3-27) days. According to stratified groups, 113 (52.6%) patients were aged ≤14 days and 102 (47.4%) patients were aged >14 days. Mean age of patients aged ≤14 days was 7.73 ± 3.71 days and for patients aged >14 days the mean age was 19.94 ± 3.54 days.

The overall mean height was 51.53 ± 1.56 cm, with range of 8 (47-55) cm. The overall mean weight was 1645 ± 393.72 grams, with range of 2355 (1002-3357) grams. The overall mean occipital frontal circumference (OFC) was 37.15 ± 1.58 cm, with range of 6 (35-41) cm. The overall mean TSH was 30.01 ± 10.89 (μU/ml), with range of 42 (10-52) (μ U/ml).

Height, weight, OFC, and TSH are stratified into groups. The results showed that height of 48 (22.3%) patients was ≤ 51 cm and height of 167 (77.7%) patients was >51 cm. The weight of 132 (61.4%) patients was ≤1645 grams and weight of 83 (38.6%) patients was >1645 grams. The OFC of 122 (56.7%) patients was ≤37 cm and of 93 (43.3%) patients was >37 cm. The TSH of 180 (83.7%) patients was ≤40 (μU/ml) and TSH of 35 (16.3%) patients was >40.

It was observed that mean height of patients with height ≤51 cm was 49.34 ± 1.22 cm and for patients with height >51 cm mean height was 52.16 ± 0.97 cm. Mean weight of patients with weight ≤1645 grams was 1442.04 ± 194.38 grams and for patients with weight >1645 grams mean weight was 1969.7 ± 413.71 grams. Mean OFC of patients with OFC 37 cm was 35.95 ± 0.81 cm and for patients with OFC >37cm mean OFC was 38.72 ± 0.77 cm. Mean TSH of patients with TSH ≤40 (μU/ml) was 27.12 ± 9.39 (μU/ml)and for patients with TSH >40 (U/ml)mean TSH was 44.89 ± 3.16 (μU/ml).

Congenital hypothyroidism was observed according to TSH value. As the results showed that 35 patients had TSH >40 (μU/ml) so the congenital hypothyroidism was observed in 35 patients. The frequency distribution is presented in Table 1 and Fig.1. The descriptive statistics of age, height, weight, OFC, and TSH of patients with positive congenital hypothyroidism are presented in Table 2. The stratification was done on gender, age, height, weight, and OFC to see the association of these with outcome in Table 3.

The results showed that among 35 positive congenital hypothyroidism patients, 19 were male and 16 were female. Age of 24 patients was ≤14 days and age of 11 patients was >14 days. Height of 15 patients was ≤51 cm and height of 20 patients was >51 cm. Weight of 23 patients was 1645 grams and weight of 12 patients was >1645 grams. OFC of 24 patients was ≤37 cm and OFC of 11 patients was >37. The results of association showed that no significant association of congenital hypothyroidism was found with age and height at p≤0.01. No significant association of congenital hypothyroidism was found with gender, weight, and OFC with p>0.05.

Discussion

Screening for congenital hypothyroidism (CH) is successfully used for the last two decades. However, this has not been completely implemented in Pakistan because of several factors like cost, lack of reliable laboratories on a large scale, and non-availability of baseline data in our population. High value of TSH more than 40 μU/ml suggest primary hypothyroidism. In secondary or central hypothyroidism TSH will be very low. In this way a low TSH level rules out secondary or central hypothyroidism[4]. Use of cord blood TSH as a screening tool is an attractive suggestion because of its simplicity and accessibility.

We used a low cut off range of TSH for screening congenital hypothyroidism in our study compared to higher range in other studies. Corbett et al[16]. showed that the use of low TSH cut off allowed the detection of an unsuspected number of children with neonatal hypothyroidism, evolving in mild permanent thyroid dysfunction later in life. In the present study TSH value up to 40 μU/ml was taken as normal and risk for CH above 40 μU/ml. Devi and Noushad[17] also had taken same comparison of TSH in their study.Recently another study from India by Gurjit Kaur et al[18]. from Chandigarh, had taken 9

μU/ml as TSH cutoff range. Rasul and Lucky[19], in their study from Bangladesh also had taken cut off range similar to the present study. Mao, Yang and Liu used TSH concentration ≥9 μU/L to reinvestigate neonates for secondary screening[20].

In the 215 neonates studied, the male were 112 (52.1%) and females were 103 (47.9%) in the present study, which is similar to previous studies[19]. Mean weight of neonates in the present study was 1564.83 ± 304gm which is in accordance with Manglik et al[21].

The characteristic sign and symptoms of congenital hypothyroidism are rarely seen in the neonatal period. This explains why, before the advent of mass screening approximately 10% of infants were diagnosed clinically in the first month and 35% within three months[22]. The age at which treatment for congenital hypothyroidism is started decides success of screening program. Treatment of congenital hypothyroidism if started before age of 3 months results in satisfactory physical and mental development in affected infants[22]. The results of our study are consistent with previous studies as significant age affect was observed in the sample. Approximately 24 neonates diagnosed clinically were aged ≤14 days and 11 neonates aged >14 days.

Screening programs for congenital hypothyroidism, based on measurement of TSH in blood can diagnose 97% of infants[23]. This has been proved by review of literature. Screening in neonatal age is most significant modality of diagnosing Congenital Hypothyroidism. However, no screening program is 100% sensitive or specific in diagnosing Hypothyroidism. Compared with prescreening period, our study has revealed 35 (16.3%) cases. The incidence is higher than that reported in other countries like Thailand[24]. However, other parts of Europe have an incidence of CH similar to ours, such as Portugal (1/2500) and Estonia (1/2860)[17].

Another problem in screening of Congenital Hypothyroidism is cut off TSH levels. It's difficult to compare results of different studies because cut off levels are different. If level of TSH ≥30 mU/ml is taken as reference, there is a chance to miss many cases. In multicenter trials it has been proved to keep cut off level of TSH as low as 10mU/ml[25]. This approach is suggested to avoid missing cases with initial borderline levels but later has persistent high levels of TSH. It is now recommended to follow-up babies with borderline levels of TSH, for a repeat test. This is recommended to avoid over diagnosis and over treating this lethal condition. In our study we used the same method of recalling babies. But contrary to other studies, our study showed only two babies with borderline TSH values on initial test that later on had persistent high levels.

Congenital hypothyroidism can result in profound cognitive and developmental delays in infants and children unless diagnosed within days of birth and treatment initiated.The incidence of congenital hypothyroidism may have doubled during the past decade, but variability of screening techniques and criteria for a positive newborn screening result vary across the United States. Paediatric primary care providers and paediatric nurses must monitor newborn screening results and make sure infants with a positive screen are seen by a paediatric endocrinologist for further evaluation. They must educate parents on the condition and importance of frequent serum monitoring of thyroid levels to assure optimal growth and development of the infant and child.

Limitation of this study included that this study was done only in well baby clinic, sick or preterm neonates should be called for follow up and test repeated if necessary. The positive cases were not followed, in this regard future studies are mandatory. Serum T3 and T4 were not done in this study because of financial constraint.

Although there is nothing new in this study but neonatal screening program is a very effective tool for early diagnosis and treatment of congenital hypothyroidism. Still many health care facilities in Pakistan are not practicing this neonatal screening program for congenital hypothyroidism and this study is carried out to emphasize the importance of this very effective tool against a treatable cause of mental retardation.

Conclusion

The screening for congenital hypothyroidism for newborns give benefit to patients and their families and provides new information regarding the epidemiology, pathophysiology, diagnosis and treatment of thyroid disease in infancy. TSH >40 μIU/ml after 2 days should be taken as a positive case and parents should be counseled about the disease, further work up and management.

Conflict of Interest

Authors have no conflict of interests and there was no grant/ funding from any organization for this study.

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