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Original Research Article

Clinical profile of congenital hypothyroidism identified through new-born screening: a retrospective observational study

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ABSTRACT

Background: Congenital hypothyroidism is one of the most common preventable causes of mental retardation. The incidence and etiology of congenital hypothyroidism varies significantly across the globe.
Methods: In this retrospective observational study we aimed to find out the incidence and etiology of congenital hypothyroidism identified by neonatal screening program. We included all neonates who had their thyroid stimulating hormone screening done in a tertiary care hospital of South India between January 2014 and June 2020 and were diagnosed as a case of congenital hypothyroidism. The growth patterns, clinical features, thyroxine dose requirement during follow-up were also studied.
Results: There were 23 babies diagnosed with congenital hypothyroidism during the study period. The incidence rate was 1 in 917 live births for inborn babies, and dyshormogenesis (60%) was the most common etiology. Two babies had clinical features associated with congenital hypothyroidism. None of the babies had clinical features of congenital hypothyroidism during follow-up and their growth & development were normal for age. Babies who required dose increments of thyroxine supplement turned out to be permanent congenital hypothyroidism.
Conclusion: Incidence of congenital hypothyroidism was high in our population. Dyshormogenesis was the most common etiology. Majority of congenital hypothyroidism babies were asymptomatic at diagnosis, so screening is a vital tool for early diagnosis. Babies who required thyroxine dose increment with age tend to be permanent congenital hypothyroidism.

Keywords: Congenital hypothyroidism, Thyroid dyshormogenesis, Thyroid dysgenesis, Dose increments, Newborn screening

INTRODUCTION

Congenital hypothyroidism (CH) is an important cause of mental retardation in children.[1] With the introduction of newborn screening, most of the babies with CH are being diagnosed during the neonatal period even before the onset of symptoms. The most commonly used screening protocol is serum thyroid stimulating hormone (TSH) measurement owing to its superior sensitivity and specificity. With the increasing neonatal screening coverage all over the world, the incidence of CH is also increasing.[2]

The incidence rate of CH varies by geographic location and ethnicity.[3] There is also significant difference in the etiology of CH based on the population being studied. Our country being a mixed population with lot of inbreeding, it will be useful if the local incidence of CH and its etiology is known for better management.

METHODS

We conducted this retrospective study in a tertiary level neonatal unit at PSG institute of medical science and research hospital, Coimbatore in South India. The primary

objective of the study was to find out the incidence and etiology of CH identified through newborn screening program. Our secondary objective was to follow-up the growth & development and to find out whether the dose requirement of thyroxine in these babies during follow-up can help us to differentiate permanent from transient CH cases. The study was approved by hospital ethical committee. All neonates (<30 days of life) from January 2014 to June 2020 (78 months) for whom TSH screening was done in the hospital were included in the study. We had excluded babies who were diagnosed and referred as a case of CH from other hospitals.

Serum TSH was used as screening tool for congenital hypothyroidism, which is measured by taking a venous blood, usually around 72 hours of life. In case of early discharge, samples were taken prior to discharge. Serum TSH, free T4 (fT4) and free T3 (fT3) were measured in hospital's biochemistry laboratory using sandwich electroluminescence immunoassay using cobas e601 (Roche Ltd). All neonates with TSH values <10 mIU/L were considered screen negative. If the initial TSH screening value was in the range of 10-39 mIU/L, then TSH value was repeated at around 14 days of age. All babies with serum TSH ≥40 mIU/L at any time or ≥10 mIU/L on two occasions were considered screen positive. Babies with very high TSH values were given a value of >100 mIU/L by the hospital biochemistry lab instead of absolute value.

All screen positive cases were evaluated with thyroid hormone profile, ultrasound (USG) thyroid and technetium (Tc-99m) pertechnetate thyroid scintigraphy. Etiological diagnosis was primarily based on scintigraphy results. If it shows increased tracer uptake, then it was considered to suggest organification defect and a diagnosis of dyshormogenesis was made. If there was ectopic tracer uptake, then ectopic thyroid was diagnosed and if no tracer uptake was seen then agenesis was considered. If only USG thyroid report was available, etiology of dyshormogenesis was made if the gland was present and dysgenesis was considered if it was absent. Treatment with levothyroxine was started as early as possible after evaluation. During follow-up, growth and development of these babies were monitored using World Health Organization (WHO) growth charts and Trivandrum development screening chart respectively.

Babies with CH were identified by scrutinizing the screen positive babies' case records from the medical records department. The clinical, demographic and laboratory data of these babies were obtained from the hospital's computerized database and baby's case records. Few babies had some data missing which were obtained through telephonic conversation with the parents. The follow up data including growth & development, clinical features of CH, TSH & fT4 values, the dose adjustments of thyroxine were all collected.

Data were entered in Microsoft excel and analyzed by Epi Info™ software. Results were presented as mean±SD or median with IQR for continuous variables and as percentage for discrete variables.

RESULTS

A total of 19282 babies were born during the study period of 78 months, among them 18349 babies (95%) had their TSH screening done and 20 babies were diagnosed as CH giving an incidence rate of 1 in 917 live births. Among the 133 out-born neonates screened in our hospital, three babies were diagnosed as CH. Thus 23 babies were diagnosed as CH overall. The baseline characteristics of these babies are given in table 1.

Table 1: Baseline characteristics of children with congenital hypothyroidism.

Characteristics	Result
Gender (male:female)	1:1.6
Day of positive screen (median, IQR)	3 (2,4)
GA in weeks (mean±SD)	38.3±1.6
Birth weight in grams (mean±SD)	2969±449
Mode of delivery	**N (%)**
Vaginal	15 (65)
Caesarean	8 (35)
Day of starting treatment (median, IQR)	3 (2,4)
No of preterm babies (<37 completed weeks)	4 (17)
No. of LBW (<2500 gm)	3 (13)

GA – Gestational age; LBW- Low birth weight.

The clinical features, thyroid function test values, USG thyroid and Tc99 radio nucleotide isotope scan reports at diagnosis are provided (table 2). Two babies had clinical features associated with CH at presentation. One baby had Down syndrome and the other presented with delayed passage of meconium. In two babies USG thyroid report showed gland in situ but did not have scintigraphy report available and an etiological diagnosis of dyshormogenesis was made. A total of twenty babies had the etiology of CH available and among them more than half of the babies (60%) were diagnosed with dyshormogenesis. Among the babies with thyroid dysgenesis (40%), ectopic thyroid was the most common etiology and all ectopic thyroids were lingual thyroid.

Only seventeen babies had both etiological diagnosis and complete follow-up details (table 3) and among them none of the babies had any growth or developmental abnormalities. More than half of these babies (59%) did not require dose increment during follow-up and among them dyshormogenesis (90%) was the most common etiology. Those babies who required dose increments during follow-up (41%) had dysgenesis as the most common etiology (72%). Among those babies who had crossed three years of age (n=8), the thyroxine

supplements were stopped in four babies and all of them had dyshormogenesis as the etiology of CH.

Table 3: Clinical and laboratory features of babies at diagnosis.

Characteristics			Results N (%)
TSH value at first screening in mIU/l (n=23)	>100		14 (61)
	40-100		4 (17)
	10-39		5 (22)
fT4 (n=21) ng/dl (mean±SD)			1.1±0.6
fT3 (n=13) pg/ml (mean±SD)			2.25±0.89
USG thyroid (n=8)	Absent		3 (38)
	Present		5 (63)
Tc99 radionucleotide scan (n=18)	Dyshormogenesis		10 (56)
	Dysgenesis (n=8)	Agenesis	3 (17%)
		Lingual thyroid	5 (28%)
Clinical features (n=23)	Asymptomatic		21 (91)
	delayed passage of meconium		1 (5)
	down syndrome		1 (5)

TSH- Thyroid stimulating hormone; USG- Ultrasonogram; Tc99- Technetium-99 isotope.

Table 3: Thyroxine dose adjustments and clinical outcome of babies in whom both the diagnosis and follow-up details are known.

Characteristics			Results N (%)
Dose adjustments (n=17)	Not required dose increment (n=10)	Dyshormogenesis	9 (90)
		Dysgenesis	1 (10)
	Dose increment at least once during follow-up (n=7)	Dyshormogenesis	2 (28)
		Dysgenesis	5 (72)
Treatment decision at 3 years (n=8)	Successfully stopped treatment (n=4/8)	Dyshormogenesis	4 (100)
		Dysgenesis	0
	Continued treatment (n=4/8)	Dyshormogenesis	1 (25)
		Dysgenesis	3 (75)

DISCUSSION

In our study, the incidence of CH was 1 in 917 and dyshormogenesis was the commonest cause. Several studies have arrived at a different incidence rate for CH. In the study conducted in United States by Waller et al,4 non-Hispanic Black had lower incidence (1 in 11494) while Asian had the higher incidence (1 in 2506) of congenital hypothyroidism. Similar difference among ethnic groups were obtained in other studies.[5,6] In the study done by Arasar Seeralar et al in Chennai, the incidence rate of CH was 1.7 in 1000.[7] Similar high incidence rates were reported in other Indian studies done in different parts of the country.[8,9] High incidence rate found in population of Iran was attributed to a closed community with high inbreeding rate.[10] In India too this could be the reason for higher incidence due to marriage within the caste/community leading to inbreeding.

This study showed that, dyshormogenesis (60%) was the most common etiology of CH in our population. On the contrary, in most of the studies done in other parts of the world, dysgenesis contributed to more than 80% of the CH cases.[11] Since most of the cases of dyshormogenesis are inherited conditions, the high incidence is expected in a closed community like our population. Among those with dysgenesis, almost two third of the babies were diagnosed as Lingual thyroid, similar to the finding reported by Castanet et al.[12] This is in contrast to the study by Devi Dayal et al, where agenesis was reported more common than ectopia.[13]

Considering the clinical features at diagnosis, most of the babies were asymptomatic (91%) underscoring the importance of screening. Two babies had clinical features associated with CH, one with delayed passage of meconium and the other had Down syndrome. Though there were three babies who had neonatal jaundice requiring treatment with phototherapy, none had prolonged jaundice which is classically described in CH. Except these two babies, rest of them would have been missed otherwise and could have potentially ended up with morbidity without the screening process.

Among the babies who required thyroxine dose increment (41%) during the follow-up, dysgenesis (72%) was the most common etiology and these babies are likely to require lifelong thyroxine supplements. In those babies where thyroxine dose requirement did not increase with age (59%), dyshormogenesis (90%) was the most common etiology. All the babies in whom the thyroxine supplements were successfully stopped at 3 years of age belonged to this group. This shows that babies who don't require dose increment turn out to be transient CH and tend to be having dyshormogenesis. A similar finding was arrived in other studies where permanent CH had increased dose requirement as age increases compared to transient CH.[14,15] In our study, the etiological diagnosis of dyshormogenesis were made based on increased iodine trapping seen in the radionucleotide studies but confirmation with genetic studies could not be done. The fallacy of this approach is that there are several causes of transient CH which presents with increased thyroid trapping by scintigraphy at diagnosis. These include maternal iodine deficiency, transient dyshormogenesis due to haplodeficiency mutation affecting DUOX2 and DUOXA2 and other genes.[16-18] In developing country like

India where nutritional deficiency is very common, one can expect that a significant proportion of these babies with increased iodine trapping in radionucleotide scintigraphy may actually be having transient CH due to maternal iodine deficiency. One baby diagnosed as agenesis by scintigraphy (USG thyroid not available) had decreased dose requirement as age increased which is not expected in a case of true agenesis. The baby's mother was diagnosed as Hashimoto's thyroiditis since her adolescence. So the initial scintigraphy finding was likely due to the TSH blocking effect of trans placentally transferred maternal antibodies.[19] So in resource limited settings where genetic diagnosis could not be done, USG thyroid along with radio isotope scan will give a reliable etiological diagnosis as compared to either of it done alone.

CONCLUSION

To conclude, the incidence of CH in our population was 1 in 917 live births. The most common etiology was dyshormogenesis followed by dysgenesis. Almost all the babies with CH were asymptomatic during neonatal period which makes screening a vital tool for diagnosis. Those babies who required increment in thyroxine dose as age increases tend to be permanent CH.

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