Original Article

Etiological Profile, Targeted Levothyroxine Dosing and Impact of Partial Newborn Screening in Congenital Hypothyroidism—A Single Centre Experience

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Abstract

Background: Congenital hypothyroidism (CH) is the most common cause of preventable intellectual disability. Newborn screening (NBS) for CH has been in vogue in many parts of the world since 1970, but despite its well-known benefits, many developing countries including India have not been able to establish universal NBS for CH till date. **Objective:** The aim of this study was to review the clinical aspects of congenital hypothyroidism in a tertiary care university referral teaching hospital, focusing on aetiology of CH, predictors of permanence, optimal targeted dose strategies based on aetiology and the effect of newborn screening on the time to diagnosis. **Material and Methods:** The electronic medical records of 233 children with CH referred to our centre between January 2009 and December 2019 were analysed. A partial NBS was established in the state in 2012. **Results:** Dyshormonogenesis (57.5%) was the most common aetiology of CH. The incidence of transient CH in children with a gland *in situ* (GIS) was 35%. Levothyroxine (LT-4) dose of >2.75 µg/kg/day (sensitivity 76.5, specificity 72), >2.15 µg/kg/day (sensitivity 82.4, specificity 61.9) and >1.85 µg/kg/day (sensitivity 76.5, specificity 61.9) at years 1, 2 and 3, respectively, were predictors of permanent CH. An initial LT-4 dose ≥8 µg/kg was sufficient and very seldom led to undertreatment in children with dyshormonogenesis. On the contrary, even doses ≥13 mcg/kg/day led to frequent undertreatment in children with thyroid dysgenesis. After the introduction of newborn screening, the median age at diagnosis came down from 45 days (IQR 14–180 days) to ten days (IQR 3–12 days). **Conclusion:** Targeted dosing based on aetiology of CH may be more appropriate to optimise outcomes. The time to diagnosis of CH reduced significantly after the adoption of even a partial NBS program highlighting the urgent need for implementation of the same in resource poor settings.

Keywords: Congenital hypothyroidism, newborn screening, overtreatment, targeted dosing, transient congenital hypothyroidism

Introduction

CH is the most common cause of preventable intellectual disability. NBS for CH has been in vogue in many parts of the world since 1970, but despite its well-known benefits, many resource poor countries including India have not established universal NBS for CH till date.[1] Kerala is a state in India with a population of close to 35 million but with health standards similar to developed countries as exemplified in its infant mortality rate of 4.4 which is at par with the US.[2,3] The government of Kerala had established NBS for CH in a limited manner in 2012 covering 40% of government hospitals and extended it to 100% of government hospitals in 2018 which covers 25% of all births in Kerala per year.[4] The remaining 75% births happen in private hospitals many of which do routine thyroid function tests on all newborn babies before discharge at the point of care. The authors have noted a definite improvement in the time of diagnosis of CH after 2012 when partial NBS was introduced.

The aim of this retrospective study was to study the clinical aspects of congenital hypothyroidism in a tertiary care

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university referral teaching hospital in the state of Kerala which happens to be the first formal paediatric endocrinology referral centre of the state, focusing on aetiology of CH, predictors of permanence, optimal targeted dose strategies based on aetiology and the effect of newborn screening on the time to diagnosis.

Materials and Methods

After institutional ethical committee clearance, the electronic medical records of 233 children with CH referred to our centre between January 2009 and December 2019 were analysed. Majority of the babies were diagnosed to have CH elsewhere and referred to our centre for further management. At our centre, CH was diagnosed as per AAP guidelines[5] till 2018 and ISPAE[6] guidelines from 2018 onwards. Venous confirmatory TSH >20 mIU/L before age 2 weeks and >10 mIU/L after age 2 weeks with low T4 was defined as primary hypothyroidism and with normal T4 as isolated hyperthyrotropinemia. Both were included as CH and were initiated with levothyroxine treatment.

The Abbott Architect assay was in use until 2017, and Roche Elecsys assay was used from 2018. The aetiology of CH was classified into dysgenesis and dyshormonogenesis. Agenesis, hemiagenesis, ectopia and hypoplasia as confirmed by ultrasonographic and/or scintigraphic findings were taken as dysgenesis. Children with CH with gland *in situ* (GIS) were considered to have dyshormongenesis. All children were treated with tablet levothyroxine sodium at a dose decided by the treating physician based on standard guidelines. Standard instructions were given to dilute the tablet in breast milk or plain water and to be administered using an infant feeding spoon (paladai). Data on undertreatment and/or overtreatment were collected based on follow-up thyroid function tests. Children with suspected dyshormonogenesis were given a trial off therapy at the age of three years according to the judgement of the treating physician.

Statistical analysis

The Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 21.0) was used for statistical analysis. Numerical variables were summarised by mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were summarised by proportions. Pearson Chi-square test was used for finding the association between two categorical variables. The doses for prediction of permanency of CH were estimated using a receiver operating characteristic (ROC) curve, and area under curve (AUC) was determined. AUC values from 0.5 to 0.7 represent low accuracy, values from 0.7 to 0.9 represent moderate accuracy, and values >0.9 represent high accuracy.[7]

Ethical Clearance Statement

The study was approved by the Institutional Ethics Committee, Amrita Institute of Medical Sciences, vide IEC-AIMS-2020-ENDO-111 on 21.07.2020.

Results

Two hundred and thirty-three children with CH were included in the study (male:female—125:108).

Effect of newborn screening

Partial NBS for CH was established in Kerala in 2012. In our cohort, 127 (54.5%) children were diagnosed after 2012, while 106 (45.5%) were diagnosed before that. The median age at diagnosis of CH before 2013 was 45 days (IQR 14–180 days). After the introduction of a partial newborn screening in Kerala, the median age at diagnosis came down to ten days (IQR 3–12 days).

Aetiology of CH

The aetiology of CH is depicted in Table 1. Dyshormonogenesis (57.5%) was the most common aetiology in our cohort.

Permanent and transient CH

A total of 77 children with GIS had completed 3 years, and L-T4 supplementation could be successfully stopped in 27 (35%). Fifty-four children with dyshormonogenesis who had completed three years had at least one follow-up at our centre before 3 years of age, and their doses at year 1, 2 and 3 were compared. Details of L-T4 doses were available in 42, 44 and 54 children at year 1, 2 and 3. Receiver operating characteristic (ROC) curve to study the various doses of LT-4 to predict permanent CH is depicted in Figure 1. A dose of >2.75 µg/kg/day (sensitivity 76.5, specificity 72), >2.15 µg/kg/day (sensitivity 82.4, specificity 61.9), >1.85 µg/kg/day (sensitivity 76.5, specificity 61.9) at years 1, 2 and 3, respectively, were predictors of permanent CH [Table 2]. Area under the curve (AUC) for doses at year 1, 2 and 3 is 0.786, 0.782 and 0.748, respectively.

Dosing of LT-4 based on aetiology

A total of 52 patients (28 males, 53.8%) with data on response to treatment at one month were identified. The baseline characteristics of the patients are summarised in

Table 1: Aetiology of CH

Aetiology	Percentage
Dyshormonogenesis	134 (57.5%)
Dysgenesis	93 (39.3%)
Agenesis	35 (15%)
Hypoplasia	22 (9.4%)
Ectopic	4 (1.7%)
Hemiagenesis	2 (0.8%)
99 m Technitium scintigraphy couldn't be done	30 (12.8%)
Consumptive hypothyroidism	1 (0.4%)
Could not be evaluated	5 (2.1%)

Table 2: Doses predicting the permanency of CH

	LT-4 dose cut-off	Sensitivity	Specificity	AUC	*P*
Year 1	>2.75	76.5	72	0.786	0.003
Year 2	>2.15	82.4	61.9	0.782	0.003
Year 3	>1.85	76.5	61.9	0.748	0.003

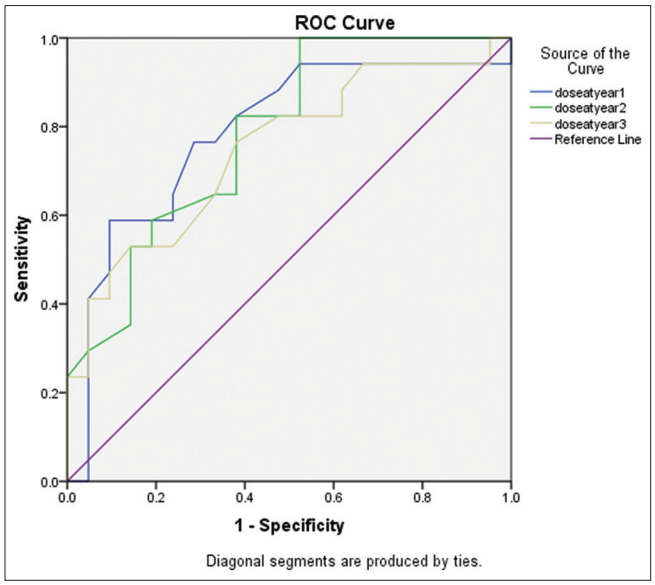

Figure 1: Receiver operating characteristic (ROC) curve of various doses of levothyroxine to predict permanent CH at ages 1, 2 and 3 years

Table 3. Majority of the patients were term infants (88.5%). The aetiology of congenital hypothyroidism was thyroid dysgenesis in nine patients (17.3%) and dyshormonogenesis in 43 patients (82.7%). Mean TSH before starting treatment was 78.61 ± 39.1 uIU/ml. The dose at initiation reflected the practice of the treating physicians and seemed to depend on the initial FT4 and TSH. The starting dose of L-T4 for patients whose TSH <100 uIU/ml and FT4 were low normal was 10.58 ± 3.79 µg/kg compared to 13.1 ± 2.40 µg/kg in patients with initial TSH >100 uIU/ml and very low FT4. (p = 0.007) The mean doses at initiation in dysgenesis (11.73 ± 3.34 µg/kg) and DH (11.76 ± 3.2 µg/kg) were similar (p = 0.06).

The patients were divided into three groups according to the initial L-T4 dose. Group 1 (n = 10) had an initial dose of 6–7.9 µg/kg. Group 2 (n = 20) had a starting dose of 8–12.9 µg/kg, and Group 3 (n = 22) had an initial dose of 13–18.5 µg/kg/day. The outcomes at 1 month after starting treatment were as follows [Table 2]: in Group 1, 30% had labs in target range, 20% (2) were overtreated, and 50% (5) were undertreated. In Group 2, 45% (9) had target labs, 45% (9) were overtreated, and 10% (2) were undertreated. In Group 3, 31.8% (7) had labs in the target range, 50% 11) were overtreated, and 18.2% (4) were undertreated.

In patients with dyshormonogenesis [Table 4], 33.3% (3), 43.8% (7) and 38.9% (7) patients had labs in the target range in groups 1, 2 and 3, respectively, at one month after starting treatment. In patients with dysgenesis [Table 5], 0% (0), 50% (2) and 0% (0) patients had labs in the target range in groups 1, 2 and 3, respectively.

Discussion

Delayed treatment of neonatal hypothyroidism may result in profound neurodevelopmental delay emphasising the need

Table 3: Baseline characteristics of the 52 patients included for aetiology-based dose evaluation

Characteristic	Value
No. of males/females	28 (53.8%)/24 (46.2%)
Term/preterm	46 (88.5%)/6 (11.5%)
Aetiology of CH	
Dyshormonogenesis	43 (82.7%)
Dysgenesis	9 (17.3%)
Mean TSH at diagnosis	78.61±39.1 uIU/ml
Mean age at start of treatment	17.57±18.16 days
Initiating dose of LT-4 based on initial TSH	
TSH <100 (*n*=28)	10.58±3.79 µg/day
TSH >100 (*n*=24)	13.1±2.40 µg/day
Initiating dose of LT-4 based on aetiology	
Dyshormonogenesis (*n*=43)	11.76±3.2 µg/day
Dysgenesis (*n*=9)	11.73±3.34 µg/day

Table 4: Aetiology vs dose: Thyroid dyshormonogenesis

Dose in µg/kg	Overtreatment	Target	Undertreatment
<8	2 (22.2%)	3 (33.3%)	4 (44.4%)
8–12.9	8 (50%)	7 (43.8%)	1 (6.3%)
13–18.5	10 (55.6%)	7 (38.9%)	1 (5.6%)

Table 5: Aetiology vs dose: Thyroid dysgenesis

Dose in µg/kg	Overtreatment	Target	Undertreatment
<8			1 (100%)
8–12.9	1 (25%)	2 (50%)	1 (25%)
13–18.5	1 (25%)	0	3 (75%)

for universal CH screening to facilitate prompt diagnosis and treatment.[8,9] Although the problem of CH in developed countries has been overcome by the deployment of NBS since 1972, the same cannot be said for most developing countries, which currently lack universal NBS programmes for CH.[1] In our study, the median age at diagnosis of patients diagnosed before introduction of NBS was 45 days (IQR 14-180 days). After the introduction of newborn screening, the median age at diagnosis came down to ten days (IQR 3–12 days).

Thyroid dysgenesis is reported as the most common aetiology of CH in western literature.[10] With increasing number of preterm and LBW infants surviving, recently published studies are reporting increase in CH prevalence predominantly due to dyshormonogenesis particularly in Asian population.[11,12] Dyshormonogenesis was the most common aetiology of CH in our series. The proportion of patients with transient CH in this study of 35% was comparable to published literature showing a transient CH proportion of 33–52%.[13-17] The current guidelines recommend that all children with CH be re-evaluated at the age of 3 years for permanency of CH.[5,6,18] However, early differentiation of transient CH may be helpful for predicting prognosis and alleviating families' psychological burden. Thus, we investigated the cut-off dose of LT-4 that might allow an

early differentiation between transient CH and permanent CH at different age groups. Previous studies investigating the cut-off dose of LT-4 to predict permanency have suggested doses ranging from 3 to 4.90 µg/kg/day with specificity ranging from 63 to 100% at the end of first year, 2.8–4.27 µg/kg/day with specificity ranging from 55.8 to -100% at the end of second year and 2.25–4.70 µg/kg/day with specificity ranging from 58.2 to 100% at the end of third year.[15,17,19,20] In our study, a LT-4 dose of >2.75 µg/kg/day (sensitivity 76.5, specificity 72), >2.15 µg/kg/day (sensitivity 82.4, specificity 61.9), >1.85 µg/kg/day (sensitivity 76.5, specificity 61.9) at years 1, 2 and 3, respectively, was predictive of permanent CH. LT-4 dose requirement above these cut-offs should alert the physician about the probable permanent nature of CH. As evidence accumulates for the dose cut-off to predict permanency, newer guidelines have recognised the need for earlier re-evaluation and recommended that if a child with no permanent CH diagnosis and a GIS requires a L-T4 dose less than 3 µg/kg per day at the age of 6 months, then re-evaluation can be done at 6 months of age.[18]

The current recommended initial dose of 10–15 µg/kg/day has a wide dosing range and frequently leads to overtreatment or undertreatment requiring frequent modification in doses. There is scarce data on targeted dosing of levothyroxine in CH to optimise outcomes. This study explored targeted dosing of LT-4 based on aetiology in CH. The first treatment goal is to rapidly increase the circulating amount of thyroid hormones, reflected by normalisation of serum TSH.[5,18] Dose of 10–15 µg/kg is a rather large dosing range and translates to huge dose differences. For example, in a child weighing 4 kgs, a dose of 10 and 15 µg/kg would translate to doses as different as 40 and 60 µgs, respectively. The optimal starting dose is still debated. Though larger doses quickly normalise TSH and T4, overtreatment is also an area of concern with studies reporting reduced IQ, aggression and delinquency in children with congenital hypothyroidism exposed to overtreatment.[21] Moreover, the benefit of using larger doses on neurocognitive outcomes is not conclusively proven. A systematic review concluded that participants who were on higher initial dose of 50 mcg/day L-thyroxine had higher full-scale IQ scores compared to participants who were on lower initial dose of 37.5 mcg/day. However, verbal IQ, performance IQ and achievement scores did not differ among the groups.[22]

In our series, a dose of 8–12.9 µg/kg was sufficient and often excessive in the treatment of CH. Vaidyanathan *et al*.[23] demonstrated that an initial L-T4 dose of 10–11.9 µg/kg resulted in a higher likelihood of achieving target labs and less overtreatment at 1 month than in those patients who started at 12–15 µg/kg. Surprisingly, patients also did well in the 6–9.9 µg/kg L-T4 doses, with the majority meeting or exceeding the target dose at 1 month. Similarly, Tuhan *et al*.[24] reported overtreatment rates to be significantly higher in the highest dose group (12–17 µg/kg/day) compared with the lowest dose group (6–9.9 µg/kg/day) (61.5% and 25%, respectively, $P < 0.05$) in patients with CH. None of the patients were undertreated in this study. These studies also reported dose variations based on the initial TSH value at diagnosis. In the study by Vaidyanathan *et al*.,[23] the 16 patients whose initial TSH was <100 uIU/L received a mean dose of 8.8 µg/kg and met or exceeded the target goal range of treatment at 1 month, indicating that a lower dose aimed at 8–10 µg/kg could be sufficient in infants with less severe CH. In the study by Tuhan *et al*.,[24] patients whose TSH levels ranged from 6 to 9.9 uIU/L received a mean dose of 8.3 µg/kg/day and met the target goal range of treatment at 1 month. Patients with initial TSH levels >75 IU/L received a mean dose of 12.4 µg/kg/day and exceeded the target goal range of treatment at 1 month. However, these studies did not study the relationship of initial TSH value with aetiology of TSH.

If thyroid anatomy is known at the time of diagnosis, it would seem reasonable that patients with CH due to dysgenesis might require more L-T4 than those with anatomically normal glands.[25] There is growing evidence for the need of tailoring the dose of LT-4 according to aetiology in CH. Delvecchio *et al*.[26] reported that the dose of LT-4 was statistically larger in athyreosis compared to dyshormongenesis even beyond 14 years of age. In a study by Hanukoglu *et al*.,[27] despite having received a higher LT-4 dose, the percentage of patients who required a dose increase in the first 6 months was significantly higher in the athyrotic group compared to the dysgenesis group. The authors suggested that the aetiology should be considered as an important determinant of treatment schedules in patients with CH. In our study, an initial starting dose ≥8 µg/kg was sufficient and very seldom led to undertreatment in patients with dyshormonogenesis. On the contrary, even doses ≥13 mcg/kg/day led to frequent undertreatment in patients with thyroid dysgenesis. As previously reported, our data seem to suggest that the gland imaging reflects a functional status. The *in situ* thyroidal tissue, although insufficient to support the full daily requirement, may have a residual activity and produce a small amount of thyroid hormones.[28,29] Based on our findings, we suggest initiating LT-4 at the lower end of the recommended dose of 10–15 µg/kg/day in children with CH with GIS. Patients with dysgenesis may require doses upwards of 13 µg/kg/day with more frequent monitoring to avoid undertreatment.

The strength of our study is the large number of patients with confirmed CH from a single centre. There are several limitations of our study. Firstly, the long-term neurodevelopmental outcomes of study participants are not known. Secondly, the number of patients with dysgenesis as the aetiology of CH was very small. Further large-scale randomised controlled trials with a larger number of patients comparing the range of starting doses in different aetiologies of CH and looking at biochemical treatment outcomes and neurodevelopmental outcomes should be planned. The study supports the notion that NBS for CH should be implemented in whatever limited manner possible in resource poor settings.

Institutional ethics committee clearance

Obtained from Institutional Ethics Committee, Amrita Institute of Medical Sciences.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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