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Neurodevelopmental profile of children with congenital hypothyroidism at 18–42 months of age: A case study from South India

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ABSTRACT

Objectives: Congenital hypothyroidism (CH) is the most common preventable cause of intellectual disability in the world. It has been shown in multiple studies that with early detection and treatment of CH normal cognitive function is attainable. The Bayley scales of infant development (BSID) have been used extensively to evaluate the developmental functioning and to assist in planning of treatment for infants with neurodevelopmental delays or disabilities. The aim of the study was to assess the neuromotor and neurocognitive development of children with CH and to correlate it with treatment initiation, duration, and normalization of thyroid stimulating hormone (TSH) post-replacement therapy.

Material and Methods: This was a cross-sectional study, where children with diagnosed CH were selected from two tertiary care centers. The children aged between 18 and 42 months were called for the neurodevelopmental assessment using BSID-III.

Results: A total of 53 children diagnosed with CH were enrolled. The mean age of children was 29.53 ± 8.7 months during the study. On evaluating the children, mean cognitive composite score (CS) was 102.83 ± 12.77. Mean language CS was 106.55 ± 19.47. Mean motor CS was 111.45 ± 16.4. We noticed that there was statistically significant negative correlation between time for normalization of TSH and BSID-III motor score ($P = 0.03$). There was no statistically significant correlation between day of initiation of treatment, initial TSH level, or dose of levothyroxine to the BSID-III ($P > 0.05$).

Conclusion: Neurodevelopmental retardation has been detected in children with CH in whom time taken for normalization of TSH was longer. Babies diagnosed with CH should be under regular follow-up for evaluation of neuromotor developmental status by a multidisciplinary team.

Keywords: Congenital hypothyroidism, Neurodevelopment, Bayley scales of infant development-III

INTRODUCTION

Worldwide, congenital hypothyroidism (CH) is the most common preventable cause of neurocognitive disability.[1,2] The incidence of CH ranges from 1 in 3000 to 4000 live births in the world.[1,2] Clinical signs and symptoms are not evident until 3 months of age in majority of newborns either due to some residual thyroid function or transplacental passage of maternal thyroid hormone.[3] CH occurs more frequently in females, with a female: male ratio of 2:1.[2] It can be either transient or permanent hypothyroidism. The task force formed by Indian Council for Medical Research (ICMR) showed that the prevalence of CH was one in 722 births and

the prevalence was calculated to be one in 1130, if babies with transient hypothyroidism were excluded from the study. Although, newborn screening for CH has been adopted in many developed countries since 1970,[4] it is still not universally adopted in India. This has resulted in missing an easy and cheaply treatable disease with resultant developmental impairment creating a considerable impact on the society and health-care expenses. In the absence of universal newborn screening in India, data is limited regarding the neurodevelopmental outcomes in children with CH. The previous studies of children with CH have described that delaying diagnosis and treatment initiation beyond the first 3 months of life are likely to result in irreversible neurodevelopmental deficits. Recent studies from around the world have also report that routine screening of newborns and treatment initiation within first week of life resulted in normal or near normal intellectual performance and growth at 5–12 years of age.[2,3] Age at initiation of treatment and compliance during the first year of life affects long-term intellectual outcome.[5] Prompt initiation of treatment and rendering the infant euthyroid as early as possible is of utmost importance as there is an inverse relationship between the age at diagnosis and IQ.[6,7] Regular monitoring of thyroid function with thyroxine dose adjustment is mandatory in infancy and early childhood to achieve normal physical growth and neurodevelopment.[8] Various scales are available for the assessment of motor and neurodevelopment in CH children. In our study, Bayley Scale of Infant Development-III (BSID-III) was used for neurodevelopmental assessment on 18–42-month-old children.

AIM

The aim of our study was to assess the effect of treatment on neuromotor and neurocognitive development of children with CH between 18 and 42 months of life and to correlate the neurodevelopment to time of initiation of treatment, time for normalization of thyroid stimulating hormone (TSH), and initial dose of levothyroxine.

MATERIAL AND METHODS

This was a cross-sectional study done at Bengaluru, South India. The study period was for one year from June 2019 to June 2020. All the children diagnosed with CH were selected from the pediatric endocrine clinic register and children between 18 and 42 months of age were called for assessment. According to study design of a single group of non-interventional clinical study, a sample size of 60 was calculated. Children who were diagnosed with hypothyroidism within 3 months of life and were on levothyroxine replacement therapy were included in the study. The children with other known causes of developmental delay including hypoxic-ischemic encephalopathy, inborn errors of metabolism, chromosomal disorders, or any other congenital anomalies were excluded from the study. Preterm children and children with seizure disorders were also excluded from the study. The study protocol was screened and approved by the Hospital Ethics Committee before commencement of study.

Methodology

All children with diagnosed CH aged between 18 and 42 months were selected from the endocrine registers of pediatric endocrinology clinics at two tertiary care hospitals in Bangalore, India. They were called for the neurodevelopmental assessment using BSID-III. Informed consent was taken from the parent/s of all children and details regarding antenatal history, delivery, and neonatal period were collected and entered in a proforma. Cognitive, language, and motor domains were assessed using BSID-III by a trained investigator. The investigator was not aware of the age at diagnosis, initial TSH level, and age of initiation of thyroxine therapy. A child was given one (1) point for the performed tasks and zero (0) for the unperformed task. All sub-tests were implemented with every child using reversal and discontinue rules, to ensure administration of the most appropriate items for each of them. The test was stopped after four consecutive zeros. A raw score was obtained for each sub-test at the end of screening. In case, a risk of neuropsychomotor development impairments was confirmed, children were referred to developmental pediatrician. The assessments were carried out in a large and well-lit room, in the presence of parents. The mean duration for entire assessment was 25 min. If the child was not cooperative due to discomfort, the assessment was interrupted and resumed as soon as it was resolved. Assessment of each child was completed on the same day. The assessment was done by a standardized evaluation form and the standardized materials contained in the original Bayley test kit. Total composite scores (CS) in each category were calculated. The scores obtained were compared with the standardized original normative cutoff scores provided in the Bayley manual. For each domain, individual scores were given as per the score sheet provided with BSID-III. A BSID-III CS of ≤70 indicated developmental delay and those children were referred to the developmental pediatrician for further assessment and follow-up.

Statistical analysis

The collected data were entered in MS Excel spreadsheet and were analyzed using Statistical Package for the Social Sciences version 21.0. Quantitative variables were assessed using Mann–Whitney test between the two groups whereas Spearman rank correlation coefficient was used to assess the correlation of cognitive CS, language CS, and motor CS with age at initiation of treatment, dose started, and time for normalization of TSH. $P < 0.05$ was considered statistically significant.

RESULTS

Parents of 53 children with CH consented for the study. The mean age of children in the study was 29.5 ± 8.7 months with 58.5% being girls and 41.5% boys. The demographical, clinical, and radiological data are represented in Table 1.

The mean age at diagnosis was 24.8 ± 60.61 days with 92.5% of them being diagnosed during newborn screening. A history of maternal hypothyroidism was present in 15.1% of children. Twelve (22.6%) children had prolonged jaundice in the neonatal period. Mean neonatal TSH was 51.2 ± 34.1 mIU/L with a range of 12–150 mIU/L. The initial TSH was measured by heel prick test beyond 3 days of life and was then confirmed by a venous sample. Mean confirmatory TSH was 39.6 ± 25.3 mIU/L with a range of 5.15–100 mIU/L. (Normal range of TSH was determined as per the age of child). Mean age of initiation of treatment was 26.6 ± 60.3 days with a mean dose of 10.6 µg/kg/day. The tests were done weekly to monitor the normalization of TSH and then 1–2 monthly till 1-year of age followed by 3 monthly thereafter. The mean time taken for normalization of TSH according to age specific target was 3.3 ± 1.2 weeks with maximum of 10 weeks in one female child who had poor compliance to therapy. While on treatment, the current mean TSH was 5.4 ± 13.1 mIU/L (Normal range 0.6–5.4 mIU/L) with a mean free thyroxine (fT4) of 1.3 ± 0.3 ng/dL (Normal range 1.1–2 ng/dL). The cause of hypothyroidism was evaluated at diagnosis by ultrasound and thyroid scan. Ultrasound neck was done in all the 53 children and the most common finding was absent thyroid gland in 29 (54.7%) children. Out of 53 children, 43 had undergone radioisotope scanning and 24 (45.3%) had agenesis followed by dyshormonogenesis in 13 (24.5%), ectopic thyroid gland in 4 (7.5%), and hemiagenesis in 1 (1.9%), respectively [Table 1].

All children in the study were assessed by BSID-III within a week of latest thyroid function report. Mean values of cognitive, language, and global motor scores were calculated for the study population [Table 2]. Mean cognitive CS of 53 cases was 102.8 ± 12.8 with one child having a score of 55 indicating cognitive delay. Mean language CS is 106.6 ± 19.5 and 96.2% of the children were in the normal range as per the standard values given in BSID-III with 3.8% of them falling in the low normal range. Mean motor CS was 111.5 ± 16.4 with one child having a score of 61 which indicates motor delay. The children with low cognitive CS and low motor CS were noted to have raised recent TSH with low normal fT4. The children having TSH within normal range were noted to have normal BSID-III scores.

The BSID scores were assessed and correlated to time of initiation of treatment, time for normalization of TSH, and initial dose of levothyroxine [Table 3]. We noticed that there was statistically significant negative correlation between time for stabilization of TSH and Bayley-III motor score (P =–0.03) which implies that early normalization of TSH resulted in a good neurodevelopmental outcome. No statistically significant correlation was seen between day of initiation of treatment, initial TSH level, or initial dose of levothyroxine to the Bayley-III scores in our study ($P > 0.05$). Our study included children who were diagnosed and initiated with thyroxine supplements before 3 months of life. Thus, if the treatment was commenced before 3 months of age, there

Table 1: Baseline demographic, clinical, and radiological profile of the study population.

Parameter	Frequency	Percentage
Age (months)		
18–20 months	14	26.42
21–30 months	13	24.53
31–40 months	19	35.85
>40 months	7	13.21
Mean±SD	29.53±8.7	
Median	30 (19–37)	
Range	18–42	
Gender		
Female	31	58.49%
Male	22	41.51%
Weight Z score		
Mean±SD	−0.44±1.06	
Median	−0.44	
Range	−3.12–1.49	
Height Z score		
Mean±SD	−0.64±1.24	
Median (IQR)	−0.69	
Range	−4.89–1.95	
Head Circumference z score		
Mean±SD	−0.64±1.24	
Median (IQR)	−0.69	
Range	−4.89–1.95	
Clinical presentation		
Poor feeding	2	3.77
Constipation	5	9.43
Decreased activity	3	5.66
Increased sleep	2	3.77
Physical finding		
No signs of CH	46	86.79
Coarse facies	6	11.32
Facial puffiness	1	1.89
Investigations		
USG neck		
Normal	20	37.74
Absent	29	54.72
Bulky gland	2	3.77
Small gland	2	3.77
Radioisotope scan		
Normal	1	2.33
Agenesis	24	55.81
Dyshormonogenesis	13	30.23
Ectopic thyroid	4	9.30
Left hemiagenesis	1	2.33

Table 2: Assessment as per BSID-III of study subjects.

Scoring system as per BSID-III	Frequency	Percentage
Cognitive CS		
Normal	52	98.11
Delayed	1	1.89
Mean±SD	102.83±12.77	
Median (IQR)	105 (95–110)	
Range	55–125	
Language CS		
Normal	53	100.00
Mean±SD	106.55±19.47	
Median (IQR)	103 (94–115)	
Range	71–206	
Motor CS		
Normal	52	98.11
Delayed	1	1.89
Mean±SD	111.45±16.4	
Median (IQR)	112 (100–121)	
Range	61–154	

BSID-III: Bayley scales of infant development-III, CS: Composite score

Table 3: Correlation of cognitive CS, language CS, and motor CS with age at initiation of treatment, dose started, and time for normalization of TSH.

Variables	Cognitive CS	Language CS	Motor CS
Age at initiation of treatment (in days)			
Correlation coefficient	−0.027	0.004	−0.023
P value[#]	0.849	0.979	0.872
Dose started (in µg)			
Correlation coefficient	−0.181	-0.109	−0.099
P value[#]	0.194	0.438	0.479
Time for normalization of TSH (in weeks)			
Correlation coefficient	−0.035	-0.113	−0.288
P value[#]	0.804	0.420	**0.037**[#]

Spearman rank correlation coefficient, [#]*P* value – degree of significance. CS: Composite score, TSH: Thyroid stimulating hormone

is no correlation between age at initiation with the motor, language, and cognitive CSs. There is a correlation between normalization of TSH and motor cumulative score, as the time for normalization of TSH increases, the motor CS decreases.

DISCUSSION

In many countries of the world, screening for CH at birth has become a standard procedure. Early diagnosis and treatment can significantly reduce severe neurodevelopmental sequelae due to CH. Many studies have confirmed the early success of newborn screening for normalizing the cognitive outcomes of children with severe primary CH. Among 53 children in our study, 98% had normal cognitive and motor scores and all 100% had normal language score. In 2015, James *et al.* conducted a study with 1387 babies with CH. They used Denver developmental screening test at 4, 6, 9, and 12 months of age. At 4 months, neuromotor delay was 33% with decrease in proportion noticed on subsequent tests. At 6 months, 22% of babies were detected to have neuromotor delay and subsequent follow-up at 9–12 months showed normal development in all domains.[9] Mild speech delay was noticed in two children in our study. Regarding thyroid function status at the time of developmental assessment, 51(96.2%) children had normal and 2 (3.8%) had abnormal TSH, but all 53 (100%) had normal free T4 value.This is comparable to 57 (96.6%) children with normal and 2 (3.4%) with abnormal TSH in the study by Gulshan *et al.*[10] The new England CH collaborative reported no learning disabilities in treated CH children at 9–10 years of age.[11] In a meta-analysis done in 1996, patients with CH detected by newborn screening and treated from early age were evaluated for neuropsychologic development. It showed a trend toward lower IQ and poorer motor skills in CH patients.[12]

Klein *et al.* were the first group to report the negative effect of CH in IQ points that showed falling trend with a 5-point decrease for every month with delay in starting treatment.[13] The literature has previously mentioned that early initiation of hormone replacement has shown to positively affect the neurodevelopment. LaFranchi and Austin did a meta-analysis study of 11 trials and observed that higher IQ was present in children in whom the treatment was started before 1 month of life.[1,14] In our study, mean (SD) treatment was initiated within 30 days of birth and cognitive, language, and motor scores were not affected by the treatment initiation time. Dimitropoulos *et al.* reported that there was no correlation between age of onset of treatment and IQ points[15] as in our study.

Time required for normalization of TSH in CH is described to be a relevant factor on neurological development. Studies done by Rose *et al.* and Gauchard *et al.* indicated that more the time required for normalization of TSH caused more severe neurological development defects.[16,17] In our study also, time required for normalization of TSH had statistically significant negative effects on BSID-III scores especially the motor CS in two patients who were not compliant to therapy. In both of them, the scores were <70 which indicates severe developmental delay as per BSID-III. In our study, the two children who were detected to have delayed development fall in outlier category in terms of time for normalization of TSH and age at diagnosis and initiation of treatment but they showed statistically significant correlation between time required for normalization of TSH and BSID-III motor score.

CONCLUSION

Early diagnosis and treatment are the key elements to prevent neurodevelopmental delay in children with CH. Neuromotor

developmental retardation has been detected in a child with CH in whom time required for normalization of TSH was longer. Thus, we should work toward making newborn screening universally available in India so as that treatment can be initiated early in life. Randomized control studies are required using the newer developmental tools for the assessment of effect of CH on neurodevelopment of children.

The limitations of the study were that it was an observational study utilizing a small study population. Another limitation was convenient sampling due to logistic reasons.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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