Original Article

Neurodevelopmental assessment of neonates with congenital hypothyroidism in a tertiary care center

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ABSTRACT

Background: Thyroid hormones play a crucial role in early neurodevelopment so that untreated severe congenital hypothyroidism (CH) results in neurological and psychiatric deficits, including intellectual disability, spasticity, and disturbances of gait and coordination. **Objective:** The aim of this study is to assess the neuromotor and neurocognitive development of babies at 12 months of age who are diagnosed to have CH and initiated on thyroxine treatment at birth. Furthermore, to estimate the occurrence of CH among babies delivered in our hospital through thyroid screening. **Study Design:** This was a descriptive study. **Setting:** The study was conducted in Sree Gokulam Medical College Hospital and Research Foundation, a tertiary care center, located in Trivandrum, Kerala. **Participants:** All babies delivered in the hospital during the study period and neonatal screening was done for CH. **Methods:** Cord blood was collected as the direct flow of blood from cord, labeled and sent to laboratory from delivery room for analysis (by *chemiluminescent* assay) of thyroid-stimulating hormone (TSH). Babies with cord blood TSH level ≥20 uIU/ml were repeated at 72 h of age for venous TSH and FT4 level. Venous TSH level ≥20 uIU/ml with low FT4 (below normal range for age) was considered as abnormal and initiated on treatment before discharge from the hospital. These babies were followed till 12 months of age for neurodevelopmental assessment. **Results:** The occurrence of CH among babies delivered in our hospital was 0.6 in 100 live births. Neurodevelopmental assessment of babies with CH on follow-up has shown normal neuromotor and neurocognition at 12 months of age with early detection and prompt initiation of L-thyroxine at a higher dose range within 5 days of age. **Conclusion:** In our study, early detection and initiation of treatment in infants with CH have shown normal neuromotor and neurocognitive development at 12 months of age.

Key words: *Cord blood, Congenital hypothyroidism, Neonate, Neurodevelopmental assessment,*

Thyroid hormones play an essential role in brain development both during pre- and postnatal life. Unfortunately, clinical symptoms are often late, and nothing can be done at that point to save these children from permanent mental and physical handicap. Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation. To identify the babies in an early stage, screening of babies in first few days of life is the only choice. Without prompt treatment, most of the affected children gradually develop growth failure, irreversible mental retardation, and a variety of neuropsychological deficits. Routine neonatal screening programs, which have been in operation over the past 4 decades in the most industrialized countries, have led to the successful early detection and treatment of infants with CH and have eliminated the severe neurodevelopmental deficits resulting from late diagnosis [1]. Studies on cognitive function in patients with CH treated soon after birth have shown that normal development can be achieved in most of the patients; although some may have subtle neurocognitive deficits [2].

Certain prenatal factors associated with neurodevelopmental deficits are etiology (dysgenesis), LBW, and severity of hypothyroidism [3]. Postnatal factors include the age of onset of treatment (>1 month), lower thyroxine dose at onset (< 8 μg/kg/day), late normalization of thyroid function (> 2 weeks after treatment), and a lower socioeconomic status [4,5]. Choosing initial dose of L-thyroxine at the higher end of the recommended range and achieving normal thyroid function at 1 or 2 weeks of therapy is important to achieve optimal neurodevelopmental outcome [6,7].

Estimates of the prevalence of CH vary according to the method of ascertainment: About 1 in 2000-3000 live births in countries with neonatal screening versus about 1 in 6700 live births before the screening era [2]. Recent reports have indicated that the incidence of primary CH may be increasing in some countries, particularly for cases with a normally located (eutopic) thyroid gland and milder dysfunction. The reasons for this remain unclear [8] but may relate to changes in screening thresholds [9,10]. The first multicentric study screening above 1 lakh neonates born throughout India was launched by the Indian Council of Medical Research National Task Force Team on Newborn Screening at AIIMS, New Delhi (2007-2012), and

the preliminary results reveal a much higher incidence of CH all over India at 1 in 1172, particularly in South Indian population (1 in 727) [11].

We planned this study to assess the neuromotor and neurocognitive development of babies at 12 months of age who are diagnosed to have CH and initiated on thyroxine treatment at birth at our center. Furthermore, to estimate the occurrence of CH among babies delivered in our hospital through thyroid screening.

METHODS

This descriptive study was conducted in SGMC hospital from January 2015 to December 2015 after obtaining approval from the Institutional Ethics Committee. All babies delivered (including babies born to euthyroid and hypothyroid mothers on L-thyroxine) during the study period were subjected to estimation of cord blood thyroid-stimulating hormone (TSH) (by electro chemiluminescent assay). Our study included all healthy term babies (≥37 weeks), preterm babies (<37 weeks), and sick babies admitted in neonatal intensive care unit (includes meconium aspiration syndrome and birth asphyxia). In preterm and sick babies requiring inotropes, venous TSH and FT4 levels were repeated at 72 h of age and at 2 weeks of age irrespective of the normal range of cord blood TSH level (<20 uIU/ml) for delayed rise in TSH level. In healthy term babies with cord blood TSH level ≥20 uIU/ml, venous TSH and FT4 were repeated at 72 h of age (before hospital discharge). Cord blood was collected as the direct flow of blood from cord, labeled and sent to laboratory from delivery room for immediate analysis (by chemiluminescent assay) of TSH.

Venous TSH level ≥20 uIU/ml with low FT4 (below normal range for age) was considered as abnormal and initiated on treatment before discharge from the hospital. In all babies, L-thyroxine was initiated in the higher dose 15 μg/kg once daily in the early morning within 5 days of birth. Venous TSH and FT4 were repeated at 2 weeks of L-thyroxine therapy for normalization of TSH and FT4 level. X-ray knee was taken in babies with elevated venous TSH (≥20 uIU/ml) to assess the severity of intrauterine hypothyroidism by the presence or absence of femoral or tibial epiphyses. Ultrasonography neck was performed to localize the position of thyroid gland. Radioisotope scan Tc 99^m (scintigraphy) thyroid scan without perchlorate discharge test was performed in babies with elevated TSH before initiation of thyroxine treatment. Babies on L-thyroxine treatment were followed up at regular intervals in the outpatient department for compliance of medication and for the assessment of neuromotor and neurocognitive development.

Denver developmental screening test (DDST-1) was performed at 4, 6, 9, and 12 months of age. DDST was done by our developmental therapist. DASII and developmental quotient (DQ) was planned at 1 year of age; however, these were not performed as all our congenital hypothyroid babies (9 babies) on L-thyroxine therapy had normal DDST in all domains of milestones at 9 months and 12 months of age. The babies on thyroxine treatment in our study will be followed for 3 years for assessment of development - DASII and DQ and the need for continuation of thyroxine treatment lifelong.

Statistical Analysis

The data were entered into the Microsoft Excel sheet, and the results were analyzed descriptively using SPSS statistics version 19. The proportion of babies with CH having neurodevelopmental impairment at 4, 6, 9, and 12 months and the frequency of occurrence of CH were calculated.

CONSENT

As screening for CH is being done in our hospital for the past 10 years, a separate written parental consent was not obtained during the study period. Parents were informed about the screening protocol at the time of delivery.

RESULTS

In our study, a total number of babies underwent cord blood TSH estimation during the study period was 1387. Out of these 1387 babies, 9 babies (0.6/100 live births) had elevated venous TSH and low FT4 at 72 h of the age and initiated on L-thyroxine treatment. None of our CH babies had birth asphyxia or critically ill to require inotropic support. We had only one preterm baby with elevated TSH level Table 1. Among 9 babies with CH, radionuclide isotope thyroid scan Tc 99^m (scintigraphy) was performed in 6 babies on postnatal day 4. Thyroid dysgenesis was detected in 4 babies, and 2 babies had organification defect. None of our babies had an absence of femoral or tibial epiphyses on X-ray knee.

In all babies, L-thyroxine was initiated in the higher dose (15 μg/kg/day) within 5 days of life. Venous TSH and FT4 were repeated at 2 weeks of L-thyroxine therapy, and we could observe TSH and FT4 in the normal range at 2 weeks of initiation of treatment. Among those 9 babies with CH, 7 (77.8%) babies were born to mothers who had normal thyroid status in the antenatal period. This could be due to the presence of subclinical hypothyroidism among mothers undiagnosed in the antenatal period.

In our study, DDST-1 performed at 4, 6, 9, and 12 months showed a mild gross motor delay in the earlier age which was later normal. At 12 months of age, all our hypothyroid babies had normal development in all domains (Table 2).

DISCUSSION

Neonatal screening programs for CH have been highly successful and economically beneficial over the past four decades. Affected children are detected very soon after birth, mostly before clinical symptoms and signs become evident. Early detection and treatment prevent morbidity, particularly neurodevelopmental disabilities. Many studies have confirmed the early success of

Table 1: Demographic details

Gestation of babies	Total number of babies	Mean gestation of babies with congenital hypothyroidism	Mean birth weight of babies with congenital hypothyroidism
Term babies	8	38 weeks	2820 g
Preterm baby	1	31 weeks	2040 g

Table 2: Neurodevelopmental assessment of babies with congenital hypothyroidism

Age in months	Neuromotor delay	Neurocognitive delay	Language delay	Personal-social delay	Proportion of babies with delay (%)
4 months	3	0	0	0	33
6 months	2	0	0	0	22
9 months	0	0	0	0	0
12 months	0	0	0	0	0

congenital screening for normalizing the cognitive outcomes of children with severe primary CH [12,13].

In our study, 4 babies were detected to have thyroid dysgenesis on radionuclide isotope thyroid scan $Tc99^{m}$, which was considered as one of the prenatal factors for neurodevelopmental deficits in CH [3]. Other prenatal factors are low birth weight (mean birth weight was 2820 gm in our study) and severity of hypothyroidism as assessed by the presence of intrauterine hypothyroidism (suggested by the absence of femoral and tibial epiphyses on X-ray knee) [3]. All our CH babies were initiated on L-thyroxine in the higher dose of range (15 µg/kg/day) within 5 days of age. Furthermore, we could achieve normal venous TSH and FT4 levels at 2 weeks of initiation of the treatment in all our CH babies including babies with thyroid dysgenesis.

Gulshan et al. have shown that administering initial dose of 10-15 µg/kg/day L-thyroxine and initiating it within the first 2 weeks of age has a better intellectual outcome compared to treatment with dose of 5-10 µg/kg/day and with an age at onset of treatment later than 14 days [7]. A similar study by Joseph R has also shown that neurodevelopmental deficits exist in children whose median age of onset of treatment was >2 weeks [4]. Since the advent of newborn screening programs in 1980's, the diagnosis and treatment of this condition are now provided in the first 2-3 weeks of birth in most of the regions. Although this is sufficient to prevent mental retardation, the children so identified as CH has mildly reduced IQs from expectation and experience subtle and specific neurocognitive deficits. This deficit is correlated with the severity of hypothyroidism at birth [14].

A long-term follow-up data on cognitive and motor function in children diagnosed to have CH and initiated on treatment within 1 month have shown that it is the severity of CH before initiation of treatment is the important factor in determining the long-term cognitive and motor outcome rather than timing of treatment initiation [5,15].

Overt and subclinical hypothyroidism is common in women of reproductive age and during pregnancy. More recently, the potential adverse impact of maternal subclinical hypothyroidism and fetal hypothyroxinemia, on neurodevelopment outcomes in the offspring, has been recognized [16-18]. In our study, among those 9 babies with CH, 7 (77.8%) babies were born to mothers who had normal TSH in the antenatal period. This could be due to the presence of subclinical hypothyroidism among mothers undiagnosed in the antenatal period.

Those neonates with CH and on regular thyroxine treatment were followed prospectively for neurodevelopmental assessment. At 4 months, the proportion of neuromotor delay was 33% with decrease in the proportion of neuromotor delay on subsequent follow-up. At 6 months, 22% of babies detected to have neuromotor delay and at 9 and 12 months follow-up showed normal development in all domains (Table 2). As studies have shown [4-7] all our CH babies received initial dose of L-thyroxine at 15 µg/kg/day and initiated treatment within 5 days of age, and we could achieve the normal TSH at 2 weeks of initiation of treatment. None of our babies had absence of femoral or tibial epiphyses on x-ray knee suggesting intrauterine hypothyroidism.

The babies on thyroxine treatment in our study will be followed for 3 years for assessment of development - DASII and DQ will be performed and to decide on continuation of thyroxine treatment lifelong.

CONCLUSION

In our study, early detection of CH through universal neonatal screening for hypothyroidism and initiation of treatment in the 1st week of age at 15 µg/kg/day with normalization of TSH at 2 weeks of initiation of treatment has resulted in normal neuromotor and neurocognitive development at 12 months of age.

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