

## High Incidence of Hypothyroidism Within a Month in Neonates with Down Syndrome Who Are Euthyroid at Birth: Results of A Prospective Study

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Received: 22 May 2021; Accepted: 14 June 2021

**Citation:** Isabell B. Purdy, Amy D. Paz, Richard D. Findlay, et al. High Incidence of Hypothyroidism Within a Month in Neonates with Down Syndrome Who Are Euthyroid at Birth: Results of A Prospective Study. J Pediatr Neonatal. 2021; 3(2): 1-4.

### ABSTRACT

The objective was to test for hypothyroidism (HYT) in infants with Down Syndrome (DS) who tested euthyroid on state newborn screening for congenital HYT. In 39 infants with DS who were euthyroid at birth, serum TSH, total T4 (TT4) and free T4 (FT4) levels were measured during 15 to 120 days of age. TSH, TT4 and FT4 were measured by standard techniques. Depending up on age specific TSH and thyroid hormone (TH) levels, babies were classified as: Euthyroid (normal TSH and normal TH), Primary HYT (high TSH and low TH), compensated HYT (high TSH and normal TH) and sick thyroid (low TSH and low TH). Comparisons among different groups were performed using two-sample t-tests. Twenty-nine babies (72%) remained euthyroid (TSH  $6.1 \pm 2.6$  mIU/ml, TT4  $10.8 \pm 1.8$   $\mu$ g/dl and FT4  $1.57 \pm 0.4$  ng/dl). Six (18%) babies developed primary HYT (TSH  $23.5 \pm 10$ , TT4  $5.1 \pm 1.2$ , FT4  $1.17 \pm 0.2$ ) within a month of life needing T4 therapy. While 4 (10%) babies developed compensated HYT (TSH  $29.3 \pm 10$ , TT4  $10.6 \pm 3.6$  and FT4  $1.83 \pm 0.3$ ), one (2.5%) had sick thyroid syndrome (TSH 4.6, TT4 4.6 and FT4 1.1). All four babies with compensated HYT were euthyroid by four months of age. Despite normal newborn screening at birth, the incidence of any HYT was much higher (28 %) than the normal neonatal population (1/2000-4000). More importantly, HYT developed within a month of age. Recommendations by the AAP about retesting TH function in infants with DS should be revised.

### Keywords

Down Syndrome, Thyroid Hormone, Thyroxine.

### Introduction

DS remains the most common chromosomal disorder affecting ~ 1 in 700 neonates in the USA [1]. Each year about 6000 babies are born in the USA with DS [1]. Although signs and symptoms vary, it is associated with dysfunction of the cardiovascular, gastrointestinal, metabolic, endocrine and CNS [1-4]. Among the endocrine disorders those affecting thyroid hormones (TH) are frequent [5-10]. There is increased prevalence of primary hypothyroidism (HYT) or compensated HYT (i.e. high TSH and normal TH) in this population [5-10]. Persistent congenital HYT, detected by newborn metabolic screening, is ~ 28 times more common among infants with DS [5-10]. Early childhood prevalence rates of any TH dysfunction in DS is estimated to be 15%, however estimates in early infancy were as high as 85% based on elevated TSH levels

obtained just after the newborn screening period [5-10]. Since TSH surge occurs shortly after birth the routine newborn screening test may not be the definitive reflection of TH for diagnosing congenital HYT. An important gap in these studies was the lack of evaluation of TH after the newborn screen and before six months of age. In a retrospective study, we reported that the incidence of primary HYT and compensated HYT in babies with DS was 17.5 % and 15 % respectively [11]. However, the incidence and timing of developing primary or compensated HYT in infants with DS who were euthyroid at birth has not been studied prospectively. This investigation was therefore undertaken to do so.

### Subjects and Methods

Electronic medical records and clinical database were used to identify infants with genetically determined (chromosome analysis) DS who were admitted to the neonatal intensive care unit at Mattel Children's Hospital at UCLA and Olive View Medical

Center between April 2013 to April 2017. All babies with DS who had normal TH function at birth as determined by the California state mandated newborn metabolic screening were eligible for the study. The Human Research Protection Program at both hospitals approved this study (# 13-000246) entitled: Optimal timing of early recognition for treatment of acquired HYT in infants with DS. Informed written parental consent in English or Spanish was obtained for each patient. Repeat laboratory tests for serum TSH, TT4 and FT4 could be obtained between two weeks to four months of age. In addition to the demographic data, other diagnoses were retrieved from the clinical database and electronic medical records. Serum TSH (mIU), TT4 ( $\mu\text{g}/\text{dl}$ ) and FT4 ( $\text{ng}/\text{dl}$ ) concentrations were measured by the standard laboratory methods well established at both the institutions [11]. Determination of serum TSH was performed by electro-chemiluminescence immunoassay on Elecsys 2010 and Cobas e411 analyzers according to the TSH assay standard against the Second International Reference Standard 80/558 and the Cobas immunoassay analyzers (Roche) methods. For the TT4 assay the cross reactivity for the rapid acting TH liothyronine triiodothyronine (L-T3) and triiodothyronine (D-T3) was 1.3% and 0.8% respectively. FT4 assay cross reactivity was 1.53% for TH L-T3 and D-T3. The results were evaluated by standards for normal age-specific ranges in normal infant population provided by our laboratories. Infants with DS were then grouped into four categories based on the plasma TSH and TH results: 1) Euthyroid: Normal TSH and TT4 and FT4, 2) Primary HYT: High TSH and low TT4 and FT4, 3) Compensated HYT: High TSH and normal TT4 and FT4 and 4) Sick Thyroid Syndrome: Low TSH and low TT4 and FT4. The senior investigator established inter-rater reliability among the research team members for data abstraction on all laboratory results and various subgroup classification.

### Statistical analysis

Infant parameters (birth weight, TSH, TT4 and FT4) were summarized using means and standard deviations. Descriptive statistics were computed for the full sample of infants, and stratification by TH status (euthyroid vs primary or compensated HYT). Comparisons among infant groups were performed using two-sample t-tests. P value < 0.05 was considered significant. Analysis was performed using SAS v 9.4 (SAS Institute Inc, Cary, NC).

### Results

We identified 42 and recruited 39 infants with DS in this study. There were 20 males and 19 females, 18 Hispanic, 3 African American, 1 Asian and 17 Caucasian. 29 babies were admitted at Mattel Children Hospital (11 in born, 18 out-born) while 10 babies were admitted at OVMC (all inborn). The mean birth weight was  $2620 \pm 870$  grams (range 595-4005). The gestational age was  $36 \pm 3$  (range 26-40) weeks. 11 babies (28 %) were operated for GI disorders mostly for duodenal atresia while 10 (25%) required cardiac surgery. 18 babies (46%) did not need GI or cardiac surgery. Table 1 depicts the TSH, TT4 and FT4 concentrations in euthyroid (29), primary (6) and compensated (4) HYT babies. One baby (2.5 %) had developed sick thyroid syndrome (TSH

4.6, TT4 4.6 and FT4 1.1). Youngest age at which a baby with primary HYT was diagnosed was fifteen days (range 15-30). It was 17 days for compensated HYT group (range 17-73 days). All four babies (10 %) who had developed compensated HYT became euthyroid by four months of age. These babies were not treated with supplemental T4. All six babies (15%) who acquired primary HYT were then treated with supplemental oral T4 in consultation with a Pediatric Endocrinologist.

	Euthyroid (1) (n=29)	Primary HYT (2) (n=6)	Compensated HYT (3) (n=4)	P Value
TSH (mIU)	$6.1 \pm 2.6$	$23.5 \pm 10$	$29.3 \pm 10$	<0.001 1 vs 2 & 3
Total T4 ( $\mu\text{g}/\text{dl}$ )	$10.8 \pm 1.8$	$5.1 \pm 1.2$	$10.6 \pm 3.6$	<0.001 2 vs 1 & 3
Free T4 ( $\text{ng}/\text{dl}$ )	$1.57 \pm 0.4$	$1.17 \pm 0.2$	$1.83 \pm 0.3$	<0.001 2 vs 1 & 3

**Table 1:** Serum TSH, Total and Free T4 in Euthyroid (1), Primary (2) and Compensated HYT (3) groups.

The number of babies enrolled in this study were not enough to determine if gender, race or other co-morbidities like cardiac or GI disorders affected the development of primary or compensated HYT.

### Discussion

This is the first prospective study where development of HYT in neonates with DS who were euthyroid at birth was examined during the first four months of life. The important finding is that neonates with DS who are euthyroid at birth are at a high risk for the development of acquired primary (15%) or compensated (10%) HYT within the first month of life. Incidence of primary HYT in the normal newborn population varies from 1 in 2000 to 4000 [5-10]. These results in the present study are comparable to a similar study from our institution [11]. In a retrospective analysis we had observed similar rates of primary (17.5 %) or compensated (15%) HYT [11]. Recent reports indicate an increasing incidence of congenital primary HYT in normal newborn babies [5-10]. It is unknown if the overall incidence of congenital HYT is also increasing among babies with DS.

The American Academy of Pediatrics recommends TH testing for infants with DS at birth and then at 6 and 12 months of age [12]. To wait until 6 months of age to retest infants with DS may not be optimal. TH are critical for the CNS development, particularly during early infancy, since they influence various aspects of neuronal function at a cellular and molecular level [5-10]. Untreated HYT will adversely affect many manifestations associated with DS during early infancy including psychomotor development, body growth and CNS maturation. It is likely HYT will not be suspected clinically in babies with DS since it is difficult to distinguish symptoms and signs related to HYT from those of DS. In particular, decreased activity, hypotonia, macroglossia and developmental delay. The universal newborn metabolic screening altered the natural history of congenital HYT

which is the most common preventable cause of mental retardation [5-10]. Risk for CNS retardation is increased if treatment for HYT is delayed beyond three months of age [7-10]. In a consensus statement made by the European investigators, in babies with DS, it is recommended to re-test serum TSH concentration at the end of the neonatal period [13]. However, no data or a reference for making such a suggestion was provided [13]. Nonetheless, based on the results of this and a previous study from our institution [11] and the consensus statement [13], it seems warranted that recommendations by the AAP are revised [12]. We propose that for the babies with DS the TSH and TH should be tested at birth and retested between 15 and 30 days of age and then every month until four months of age.

The etiology of primary HYT in older children with DS is due to abnormal autoimmune function [5-9]. In the present study, development of primary or compensated HYT was observed among 18 and 10 % of neonates respectively before one month of age. Mechanisms of primary or compensated HYT remain unknown and need further investigation.

Infants with DS have a greater prevalence of compensated HYT during the first few months of life [5-9]. Compensated HYT in children with DS has been typically reported in later childhood with wide variability in range from 6 to 30% and higher [5-10]. The natural progression of compensated HYT includes conversion to euthyroid or primary hypothyroidism state [5-6]. In the present study all four patients diagnosed with compensated HYT within a month of age were euthyroid by four months of age. Because of the transient course noted in several studies it is common practice not to treat these babies with supplemental T4 [5-9]. Furthermore, treatment does not necessarily seem to impact growth and development [6]. Therefore, we chose not to treat these neonates with supplemental T4.

It would have been ideal, but we could not justify frequent blood draws in normal babies between two weeks and four months of age. Therefore, babies who remained euthyroid served as the control. We did not measure serum TSH or TH levels beyond four months of age since the AAP recommends retesting at six months of age. We recognize the need for further studies to more fully understand the mechanisms of early primary or compensated HYT with DS and to prospectively examine the potential impact on long term CNS development. Early treatment of HYT in otherwise normal babies with supplemental T4 prevents brain damage [5-9]. With earlier rescreening, T4 treatment could potentially be offered during the neonatal period in children with DS and may improve psychomotor development and growth. However, it is unknown if earlier recognition and treatment of primary HYT would improve long term neurologic outcome in this population. In the study by van Trotsenburg, the TH hormone status of neonates with DS prior to supplementing T4 was not established [14]. It is likely some babies with normal TH function were treated unnecessarily. Side effects of T4 therapy are not benign.

## Summary

The results of our prospective study further confirm finding of our previous retrospective study [11]. In neonates with DS, despite a normal TSH and TH test on newborn screening, primary or compensated HYT is more common and occurs much earlier than previously recognized. These studies should provide the basis for revising the TSH and TH function retesting in babies with DS who are euthyroid at birth. We welcome and further support the new consensus recommendation which will help in improving the health of the neonates with DS [13].

## Acknowledgements

We thank all parents for allowing their children to participate in the study. We are very thankful to Miss Michelle Oishi in coordinating the entire study. Without her help this study would not have been possible. This research was supported by funds from the divisions of Neonatology.

## Author contributions

While Dr. Purdy and Dr. Devaskar were the PI and the Co-PI at Mattel Children's hospital, Dr. Paz and Dr. Findlay were PI and Co-PI at OVMC. Dr. Purdy and Dr. Devaskar wrote the study protocol, the IRB application and the parental consent form. Mr. Ram Vangala did the statistical analysis. Dr. Devaskar wrote the manuscript which was then reviewed by all other authors.

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