RESEARCH PAPER

Neurodevelopmental Evaluation of Very Low Birth Weight Infants With Transient Hypothyroxinemia at Corrected Age of 18-24 Months

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Objective: To perform neurodevelopmental evaluation at 18 to 24 months' corrected age in very low birth infants (VLBW) with transient hypothyroxinemia.

Design: Cohort study.

Setting: Maternity teaching hospital.

Patients: Premature infants who were previously evaluated for thyroid hormone values in the first weeks of life were included.

Intervention: Data of these infants who weighed ≤1500 g and ≤32 weeks of gestation were retrieved for the current study. Available subjects (*n*=56) were evaluated for neurodevelopmental status at 18 to 24 months of corrected age. Bayley Scales of Infant Development –Second Edition (BSID-II) was performed to define Mental developmental index (MDI) and Psychomotor developmental index (PDI).

Results: The mean MDI and PDI scores were similar between the infants with and without transient hypothyroxinemia of prematurity (THOP) [79.9 ± 14.9 *vs* 70 ± 20.7, respectively (*P*=0.54); and 92.2 ± 16.4 *vs* 85.6 ± 18.9, respectively (*P*=0.68)]. After adjustment for gestational age and multiple prenatal, perinatal, and early and late neonatal variables, THOP was not associated with an increased risk of disabling cerebral palsy, or a reduction of MDI and PDI scores.

Conclusions: THOP may not be an important cause of problems in neurologic and mental development detected at the age of 18 to 24 months' corrected age.

Key words: *Neurodevelopment, Newborn, Outcome, Transient hypothyroxinemia of prematurity, Turkey*.

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Transient hypothyroxinemia of prematurity (THOP) is frequent among very low birth infants (VLBW) and is considered as a benign developmental phenomenon, an expression of temporary hypothalamic-pituitary immaturity. There is a controversy whether THOP is associated with long term sequelae and requires thyroid hormone replacement [1,2]. A previous double-blind trial of thyroid supplementation did not improve the developmental outcome at 24 months [3]. However, thyroid supplementation was found to be beneficial for children <29 weeks' gestation, especially those of 25/26 weeks' gestation, at early school age [4].

In this study, we studied the relation between THOP experienced in the first weeks of life, and neurodevelopmental disabilities when the children were 18 to 24 months' corrected age.

METHODS

This prospective cohort study was conducted in the Ministry of Health Zekai Tahir Burak Maternity Teaching Hospital. In a previous study [5], infants with a gestational age of less than 33 week were enrolled between March 2008 and February 2009, and 200 infants were available at 1st week of life. The data were available for 196, 182, and 172 infants at postnatal 1st, 2nd, and 3rd-4th week of life, respectively (***Fig.* 1**). Perinatal data of the mother and the baby was also collected from the records. In the current study, we restricted our analysis to 116 newborns weighing ≤1500 g and born ≤32 weeks of gestation. A comprehensive neurodevelopmental assessment was performed on the surviving and available 56 infants at 18 to 24 months' corrected age.

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Neurodevelopmental evaluation: During the study period, the Bayley Scales of Infant Development–Second Edition (BSID-II) was administered by experienced testers [6]. The BSID-II gives two main scales: the mental developmental index (MDI) and the psychomotor developmental index (PDI). MDI and PDI scores of 100±15 represent the mean±1SD. Cerebral palsy was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone

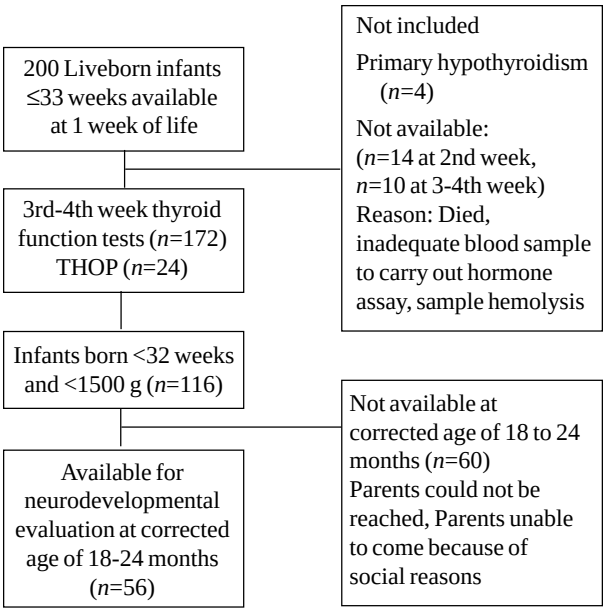

FIG. 1 *Study flow diagram.*

in at least one extremity and abnormal control of movement and posture that interfered with or prevented age-appropriate motor activity. Children with moderate-to-severe cerebral palsy were nonambulatory or required an assistive device for ambulation. Bilateral severe hearing loss was defined as permanent hearing loss that required amplification in both ears. Bilateral blindness was defined as the absence of functional vision in either eye. Neurodevelopmental impairment was defined as any of the following: moderate-to-severe cerebral palsy, an MDI or PDI of less than 70, bilateral deafness, or bilateral blindness. Profound impairment was defined as an MDI of less than 50 or a Gross Motor Function Classification System level of 4 or 5. Minimal impairment was defined as a MDI or PDI scores between 70-84 and not having moderate-to-severe cerebral palsy, bilateral severe hearing loss, or blindness [7].

We had defined THOP as T4 <25th percentile, with a normal TSH value at 1st week of life. However, we evaluated the effects of both low T4 and fT4 values on neurodevelopmental outcome at 18-24 months' corrected age [8].

Statistical analysis: SPSS 17.0 (SPSS, Chicago ILL, USA) was used for statistical analysis. Differences for continuous variables between two groups were analyzed by Student *t* or Mann-Whitney U tests according to spread of data. Chi-square test analyses were used to evaluate group differences in the binary (present/absent) medical morbidities. Pearson or Spearman correlation tests were used to analyze relation between thyroid hormone values and BSID-II scores. Logistic regression model was developed to evaluate the independent risk for unimpairment or minimally impairment, and neurodevelopment impairment. Test variables included the following perinatal variables: gestational age, gender, intracranial hemorrhage (ICH) ≥grade II, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), sepsis, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) and also included T4 <25th percentile (<68 nmol/L) at 1st and 3rd -4th week of life, and fT4<25th percentile (<13.4 pmol/L) at 1st and 3-4th week of life. A two-tailed significance level of 0.05 was applied to all analyses.

The study was approved by the Local Ethics Committee on Medical Research Ethics of The Ministry of Health Zekai Tahir Burak Maternity Teaching Hospital, Turkey. Parents of all subjects provided signed informed consent.

RESULTS

56 infants (53.6% male) were evaluated at 18 to 24 months' corrected age. The mean birthweight was 1198±194 g and gestational age 29.4±1.7 week. The

TABLE I RELATION OF NEURODEVELOPMENTAL STATUS AT 18-24 MONTHS CORRECTED AGE WITH THYROID HORMONE PERCENTILES AT 1ST WEEK OF LIFE

	T_4		*P value*	*fT_4*		*P value*
	< 25th percentile n=16	*≥25th percentile n=40*		*< 25th percentile n=15*	*≥25th percentile n=41*	
MDI, point, mean ± SD	79.9 ± 4.9	70 ± 20.7	0.36	76.6 ± 19.2	77.4 ±19.3	0.87
PDI, point, mean ± SD	92.2 ± 6.4	85.6 ± 18.9	0.17	88.2 ±16.5	87.2 ± 19.2	0.52
Minimal impairment, *n* (%)	7 (43.8)	3 (7.5)	0.003	2 (13.3)	8 (19.5)	0.71
Neurodevelopmental Impairment, *n* (%)	4 (25.0)	24 (60.0)	0.04	8 (53.3)	20 (48.8)	1.00

Neurodevelopmental evaluation done by Bayley Scales of Infant Development – Second Edition (BSID II); MDI: Mental Developmental Index; PDI: Psychromotor Developmental Index; T_4:Thyroxine levels; fT_4: free T_4.

TABLE II RELATION OF CLINICAL AND LABORATORY VARIABLES WITH NEURODEVELOPMENTAL IMPAIRMENT

	Minimal impairment	*P value*	*Neurodevelopmental impairment*	*P value*
	OR (CI 95%)		*OR (CI 95%)*	
Gestational age, wk	1.1 (0.5-2.4)	0.69	1.3 (0.8-2.0)	0.16
Gender (male)	0.2 (0.05-1.3)	0.11	1.4 (0.6-3.0)	0.33
Intracranial hemorrhage ≥grade II	1.9 (0.4-6.5)	0.39	1.4 (0.5-3.7)	0.42
Respiratory distress syndrome	10.2 (0.3-353)	0.19	0.8 (0.2-2.4)	0.74
Patent ductus arteriosus	0.18 (0.01-3.0)	0.23	2.8 (0.5-14.1)	0.19
Sepsis	1.7 (0.4-6.5)	0.38	0.5 (0.2-1.1)	0.12
Necrotizing enterocolitis	0.9 (0.2-4.5)	0.94	0.7 (0.3-1.8)	0.76
Bronchopulmonary dysplasia	4.1 (0.2-79)	0.34	0.6 (0.1-2.5)	0.49
Retinopathy of prematurity	131.8 (0.0-2.6)	0.86	0.7 (0.1-3.9)	0.70
Thyroid hormones				
T_4<25th percentile at 3rd-4th wk	2.2 (0.3-14.8)	0.38	0.7(0.2-2.0)	0.63
FT_4<25th percentile at 3rd-4th wk	4.0 (0.2-68.8)	0.33	1.1(0.5-2.6)	0.73

mean age at follow up was 21.0±1.9 months. Perinatal data were similar in children who could not be evaluated at 18 to 24 months' corrected age. Demographic and clinical characteristics of the study subjects according to thyroid hormone percentiles at 1st week of life are summarized in ***Table* I**.

The mean MDI scores were similar between the infants with and without THOP at 1st week of life (79.9±14.9 *vs* 70±20.7, respectively) (*P*=0.36). There was also no difference between these groups according to PDI scores (92.2±16.4 *vs* 85.6±18.9, respectively) (*P*=0.17). MDI scores were <70 in 22 (39.2%) and PDI scores were <70 in 10 (17.8%) of the study infants. There was disabling cerebral palsy in 7 (12.5%) infants. Neurodevelopmental impairment was present in 28 (50.0%) infants. There was no infant with bilateral hearing loss or blindness; profound impairment was also not observed. Minimal impairment was present in 10 (17.9%) of the subjects. Neurodevelopmental evaluation at 18 to 24 months' corrected age and its relation with thyroid hormone percentiles at 1st week of life are summarized in ***Table* II**.

There were no correlations between T_4 values at 1st week and MDI and PDI scores at 18 to 24 months' corrected age (*P*=0.17 and *P*=0.17). MDI and PDI scores were not correlated with gestational age, (*P*=0.28, and *P*=0.78), but positively correlated with each other (*P*=0.001). In logistic regression model, after adjustment for selected clinical variables, low T_4 or low fT_4 values at 3rd-4th week of life were not associated with an increased risk of minimal or neurodevelopmental impairment (***Table* III**).

Although we did not assess attention deficit, there were no association between BSID-II scores and thyroid hormone levels or medical morbidities.

DISCUSSION

This cohort study sought to investigate whether THOP experienced in the first weeks of life in VLBW infants would result in neurodevelopmental deficits at 18 to 24 months' corrected age. As it was proposed that developing brain depended on circulating fT_4 for local intracellular T_3 generation and fT_4 levels should be addressed when considering the effects of thyroid hormone on brain development (8). Therefore we also presented data on fT4 levels in addition to T_4.

Although the importance of thyroid hormones to perinatal neural development is well defined, their relation to the developmental sequelae of preterm birth remains unclear [9,10]. It was suggested that low plasma thyroxine concentrations could well be a preventable factor contributing to the developmental delay in VLBW infants [11]. In this study, at 18 to 24 months' corrected age, we did not find any association between THOP and neurodevelopmental disability. Our findings are not consistent with some studies [2,12] in which preterm infants with very low thyroid hormone concentrations had significantly poorer motor and cognitive outcomes than other infants.

Previous studies have shown that infants born <30 weeks gestation are at a high risk of neurocognitive impairment [13,14]. Simic, *et al*. [15] showed that it was not gestational age alone, but gestational age plus low thyroid hormone, and presence of certain medical

WHAT IS ALREADY KNOWN?

- Thyroid hormones affect brain growth and are essential to normal behavioral and intellectual development.

WHAT THIS STUDY ADDS?

- Transient hypothyroxinemia without TSH elevation may not be an important cause of problems in neurologic and mental development detected at 18 to 24 months' corrected age.

morbidities that contributed to a significant proportion of variance in these measures. They compared infants born 24 to 35 weeks gestation with healthy full-term infants at 3 months corrected age, and found that preterm infants scored significantly below full-term on BSID-II MDI and PDI, selective, sustained and total attention scales. Williams, *et al*. [16] also demonstrated an association between reduced thyroid hormone levels and the presence of PDA and infection in preterm infants. In this study, MDI and PDI scores were not correlated with gestational age in VLBW preterms. Among evaluated infants, according to 1st week thyroid hormone percentile groups, gestational age was lower in infants with T_4<25th percentile (THOP).

In a recent follow-up study of a cohort of infants born at ≤34 week gestation in Scotland from 1999 to 2001, the authors measured scores obtained from the McCarthy scale adjusted for 26 influences of neurodevelopment including parental intellect, home environment, breast or formula fed, growth retardation, and use of postnatal drugs [17]. Infants with hypothyroxinemia defined as T_4 levels 10th percentile on days 7, 14, or 28 corrected for gestational age scored significantly lower than euthyroid infants. After adjustment for confounders of neurodevelopment, hypothyroxinemic infants scored significantly lower than euthyroid infants on the general cognitive and verbal scales.

The strength of our study includes combining assessment of thyroid hormone levels at two time points with a detailed neurodevelopmental evaluation. Nevertheless, there are several limitations of this study. Firstly, the overall sample size was relatively small, involving only 56 VLBW infants. Many parents could not come to the hospital because of family reasons and soicoeconomical problems. Secondly, T_4 supplementation was not given to the study infants in the 1st weeks of life. Therefore, we could not evaluate the effect of thyroid hormone supplementation on neurodevelopmental outcome.

Reduced levels of thyroid hormone with a normal TSH values in the first weeks of life in VLBW infants are not associated with neurodevelopmental impairment at 18 to 24 months' corrected age. Further studies are needed to define other factors affecting neurodevelopmental outcome.

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