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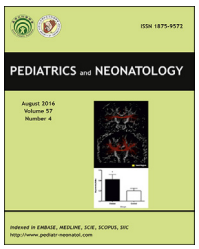

ORIGINAL ARTICLE

Three-year follow-up of children with abnormal newborn screening results for congenital hypothyroidism

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Key Words
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Background: To analyze predictive factors suggesting transient congenital hypothyroidism (TCH) compared to permanent congenital hypothyroidism (PCH) or transient thyroid function test (TFT) abnormalities among children who had positive screening results at our centers over the past decade.
Methods: A retrospective chart review of 105 subjects who presented elevated TSH levels on a newborn screening test (NST) was done. TCH was defined when a trial-off therapy was successful, and PCH was defined when a trial failed or when the subject was kept on medication beyond 3 years of age. A transient TFT abnormality was defined when follow-up TFTs were normalized without levothyroxine (LT4) therapy.
Results: Congenital hypothyroidism (CH) was diagnosed in 75.2% (TCH 35.2% and PCH 40.0%) of all subjects; the others (24.8%) showed transient TFT abnormalities. Initial NST-TSH levels (optimal cutoff point, 31.0 μIU/mL), the LT4 dose at 2 years of age (4.1 μg/kg/day), and the maximal LT4 dose (50 μg/day) merged as significant predictive factors discriminating between TCH and PCH. The initial serum level of free T4 (1.06 ng/dL) and not TSH (27.2 μIU/mL) was the only discriminating factor between transient TFT abnormalities and TCH.
Conclusion: Earlier re-evaluation might be possible when a patient's initial NST-TSH levels and maximal or 2-year LT4 doses are low, as both are important predictors of successful trial-off therapy in CH patients. When the initial serum level of free T4 is above the average value in neonates with mildly elevated TSH levels, TFTs may be more likely to normalize on their own.

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1. Introduction

Congenital hypothyroidism (CH) is typically characterized as an endocrine disorder, and it appears to be the most common preventable cause of mental retardation.[1] A newborn screening test (NST) is used to detect CH, which is confirmed by abnormal levels of serum thyroid-stimulating hormone (TSH) and free thyroxine (free T4) levels. According to the literature, CH occurs in approximately 1 in 3000–4000 live births,[2] but estimates of the incidence of CH vary according to the measurement methods used: the estimated incidence is greater than 1 in 2000–3000 live births in countries that use NST *vs.* approximately 1 in 6700 live births before the screening era.[3]

The NST program for CH, which uses TSH as a biomarker, was introduced in Korea in 1991. It became a free screening in 1997 as a Mother and Child Health project,[4] and the ratio of newborns tested to live births is now over 98% (Table 1). The reported incidence of CH in Korea has been increasing over the past decade, from 1 in 5449 newborns tested in 2004 to 1 in 1231 newborns tested in 2012 (Table 1). Considering that the number of patients with a final diagnosis of CH was based on registration data from the public health center, the actual incidence of CH is estimated to be higher. Screening results for CH are considered positive when the bloodspot TSH concentration exceeds 20 μIU/mL.[2] In Korea, a total of 13 laboratories perform the NST-TSH, and the cutoff levels of TSH vary from 10.0 μIU/mL to 22.5 μIU/mL according to each laboratory protocol.

Treatment with levothyroxine (LT4) for CH must be initiated rapidly to optimize neurocognitive outcomes[1,2] and should be continued to ensure normal growth and development during infancy. However, not all children with CH require lifelong hormone replacement therapy. Some undergo a successful trial-off-therapy at 2 or 3 years of age. Consequently, transient hypothyroidism has become a common condition in parts of the world where NST is routinely provided to all newborns.[5] The current guidelines for the diagnosis and management of CH are well organized,[1] but some details still warrant discussion.[6] For example, the increasing number of premature neonates with thyroid function abnormalities requires distinct diagnostic criteria and treatment protocol. There is also persistent confusion regarding the screening methodology that is most sensitive and cost effective. Because treatment ends before the third year of life in cases of transient hypothyroidism[6] and because studies have highlighted the negative impact of overtreatment with LT4 on developmental outcomes,[7] an earlier trial-off-therapy should be reconsidered in cases of transient hypothyroidism.

In this study, we investigated the clinical characteristics of subjects seen at our center in the past decade who had positive NST results and were found to have transient congenital hypothyroidism (TCH), permanent congenital hypothyroidism (PCH), or transient thyroid function test (TFT) abnormalities. Then, we aimed to determine the factors that predicted TCH *vs.* PCH or transient TFT abnormalities in Korean children.

2. Methods

2.1. Subjects and methods

Between July 2004 and July 2014, 105 subjects (50 boys and 55 girls) from Hallym University Medical Center and Seoul National University Bundang Hospital who had elevated TSH levels on their NST were enrolled. CH was diagnosed for subjects who started LT4 replacement therapy due to low serum levels of free T4 (<0.7 ng/dL) or elevated serum

Table 1 Newborn screening status and the incidence of congenital hypothyroidism in Korea (provided by Planned Population Federation of Korea).

Year	Number of newborn screening tested (n)	Ratio of newborn tested to live births (%)	Positive result of CH in NST (n)	Number of the final diagnosis of CH (n)	Incidence of CH (one patient per newborn tested)
2004	386,889	81.8	not available	71	5449
2005	412,653	94.9	not available	73	5653
2006	433,331	96.7	1349	144	3009
2007	472,055	95.7	1769	149	3168
2008	454,614	97.6	2015	96	4736
2009	439,387	98.8	2221	153	2872
2010	471,632	99.5	2255	163	2893
2011	465,175	98.7	2447	378	1231
2012	482,737	99.6	3028	381	1267
2013	429,759	98.4	2139	317	1356

Abbreviations: NST, newborn screening test; CH, congenital hypothyroidism.

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