The clinical course of newborn with abnormal thyroid screening test

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The clinical course of newborn with abnormal thyroid screening test

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In addition, let me extent my sincerest thanks to all professors and doctors in pediatrics who made the study in graduate school possible, interesting and very knowledgeable. And finally, I bow my head for my parents who continuously prayed for me and gave the greatest support ever.

To all the kids that are still in the hospital taking treatment I wish a quick recovery and healthy future.

LIST OF FIGURES

LIST OF TABLES

The clinical course of newborn with abnormal thyroid screening test

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Congenital hypothyroidism (CH) has an incidence of 1 in 4000 infant, and can lead to serious mental and physical impairments, if untreated. We aimed to analyze thyroid screening data of newborns at Severance Hospital from 2001 to 2005, and to follow the clinical course of infants referred for abnormal thyroid screening test. By comparing transient and permanent hypothyroidism, we sought to establish guidelines for early diagnosis, with the goal of shortening the medication period.

We calculated an average incidence of 1 per 3,774 newborns born in severance hospital. Among 76 referred patients, transient and permanent hypothyroidism was diagnosed upon follow-up in 42 (55.3%) and 29 (38.2%) patients, respectively. Etiology of permanent hypothyroidism, based on radionuclide scans and ultrasonography, included agenesis (n=10, 13.2%), hypoplasia (n=3, 3.9%), ectopic (n=6, 7.9%), and dyshormonogen esis (n=10, 13.2%). Thyroidbinding globulin deficiency was noted in 5 infants (n=5, 6.6%). Compared to transient hypothyroidism, there were

more females with permanent hypothyroidism (1.54 vs. 0.55, P=0.015). A higher frequency of additional birth defects was found in transient hypothyroidism than permanent hypothyroidism (10.3% vs.3.1%, P < 0.01). A significantly increased frequency of family history of thyroid disease was reported in children with transient hypothyroidism (6.9% vs. 32.3%, P = 0.03). In infants with transient hypothyroidism, mean screening TSH (blood spot) was significantly lower than in those with permanent hypothyroidism (152.47 vs. 45.91 p<0.01) and follow-up TSH was significantly lower than in permanent hypothyroidism (110.07 vs. 52.43, p<0.01). Mean free T4 levels were significantly lower in permanent hypothyroidism than in transient hypothyroidism (0.61 vs. 1.33, p=0.04).

Our results suggest multiple risk factors for permanent hypothyroidism such as female sex, multiple defects, a high TSH level, and a low fT4 level, compared to male sex and maternal thyroid history for transient hypothyroidism.

Key words : thyroid screening, transient hypothyroidism, permanent hypothyroidism

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I. INTRODUCTION

Congenital hypothyroidism (CH) is usually sporadic, and has an incidence of 1 in 4000 infants[1]. The most common cause is thyroid dysgenesis (80-85% of cases), either agenesis or hypoplasia, occurring from complete or partial absence of thyroid tissue respectively. Inborn errors of thyroid hormonogenesis are responsible for the remaining 10-15% of cases. In addition, transient hypothyroidism occurs in 5-10% of infants, which causes iodide deficiency or overload.

Untreated, CH can lead to serious mental and physical impairments, preventable with early diagnosis and treatment[2]. Since 2001, nationwide efforts have began to promote neonatal screening programs. Reevaluation of CH usually occurs at 2-3 years of age, after a 30-day trial of L-thyroxine discontinuation. If evaluation shows normal thyroid function,

physical, and mental development, transient hypothyroidism can be diagnosed and therapy discontinued. In the case of abnormal thyroid function, permanent hypothyroidism is diagnosed, and continuing medication is recommended. Currently, with this protocol, there is no means of distinguishing transient from permanent hypothyroidism before reevaluation at 2-3 years of age therefore the psychological and economic burden for affected children and families is prolonged.

We aimed to analyze thyroid screening data of newborns at Severance Hospital from 2001 to 2005, and to follow the clinical course of infants referred for abnormal thyroid screening test. By comparing transient and permanent hypothyroidism, we sought to establish guidelines for early diagnosis, with the goal of shortening the medication period.

II. MATERIALS AND METHODS

1. Materials

We conducted a retrospective chart analysis on two groups of patients.

The first chart analysis reviewed approximately 3,774 children, born at Severance Hospital, who took part in neonatal screening between January 2001 and October 2005.

The second review included charts from 76 neonates referred to Severance Hospital for abnormal neonatal screening at outside hospitals from January 2001 to December 2004.

The female to male ratio was 1.03, mean gestational age was 39.4 weeks, and the mean birth weight was 3.25 kg.

2. Methods

Venous T4 and TSH or only TSH concentrations, were measured after 48 hours of age. Evaluation was implemented, based on T4 <6.5ug/dl, fT4<0.7ug/dl, or TSH>20mIU/l. L-thyroxine therapy was started if abnormal levels remained at 2-6 weeks of age.

We diagnosed two different types of CH after reevaluation at age 2 to 3. In cases of continued abnormal thyroid function, following a 30 day trial off L-thyroxine, permanent hypothyroidism was diagnosed, and the existence of a thyroid gland by radioiodine scanning (^{123}I) and ultrasonogrphy was ascertained. Transient hypothyroidism was diagnosed if thyroid functionand physical and mental development were normal after discontinuing treatment.

3. Statistical analysis

Values were reported as the mean ± SD. Data was analyzed, using SPSS (version 12.0). A P value <0.05 was considered statistically significant.

III. RESULTS

1. CH prevalence at Severance Hospital

Five of approximately 3,774 children screened had an abnormal thyroid finding. At follow-up, three cases had normal TSH and fT4 levels and were diagnosed with transient hypothyroidism. One case was diagnosed with permanent hypothyroidism, and one child was lost to follow-up. We calculated an average incidence of 1 per 3,774 newborns.

2. CH prevalence in referred neonates

Among 76 referred patients, transient and permanent hypothyroidism was diagnosed upon follow-up in 42 (55.3%) and 29 (38.2%) patients, respectively (Table 1). Etiology of permanent hypothyroidism, based on radionuclide scans and ultrasonography, included agenesis (n=10, 13.2%), hypoplasia (n=3, 3.9%), ectopic (n =6, 7.9%), and dyshormonogenesis (n=10, 13.2%). Thyroidbinding globulin deficiency was noted in 5 infants (n=5, 6.6%).

Table 1. Diagnosis of referred neonates with abnormal thyroid screening .

Classification	Number(n)	Percent(%)
Transient hypothyroidism	42	55.3
Dysgenesis*	19	24.4
Dyshormonogeneis	10	13.2
TBG deficiency	5	6.6
Total	76	100

* Dysgenesis (agenesis n=10, 13.2%,Hypoplasia n=3, 3.9%, Ectopic n=5, 13.2%)

3. Demographics

Clinical characteristics of patients are listed in Table 2. Compared to transient hypothyroidism, there were more females with permanent hypothyroidism (1.54 vs. 0.55, P=0.015). No statistically significant difference was found in birth weight (3.23 kg vs. 2.94 kg), frequency of twin gestation (6.9% vs. 3.1%), or mean gestational age (39.96 weeks vs.

37.34 weeks), although a higher percentage of children with permanent hypothyroidism were delivered after 42 weeks (10.3% vs. 0%). Although not statistically significant, the proportion of premature births (less than 2500g) was higher in cases with transient hypothyroidism (0% vs. 6.3%), and the age of the mother was slightly higher in cases with permanent hypothyroidism (33.4 years vs. 31.6 years). A higher frequency of additional birth defects was found in transient hypothyroidism than permanent hypothyroidism (10.3% vs.3.1%, $P < 0.01$). Three children with permanent hypothyroidism also had either Down syndrome, William syndrome, or multicystdysplastic kidney. In transient hypothyroidism, one case of ventricular septal defect was noted.

Table 2. Clinical characteristics of permanent and transient hypothyroidism.

characteristics	Permanent hypothyroidism	Transient hypothyroidism	P-value
Female/Male	18/11(1.64)	20/22(0.91)	0.015
Gestational age(wk)	39.96 ± 2.23	37.34 ± 2.61	NS
Birth weight(kg)	3.23 ± 0.29	2.94 ± 0.54	NS
Mother's age(yr)	33.4 ± 5.34	31.6 ± 4.53	NS
Twin(n)	2(6.9%)	1(3.1%)	NS
Birth defect(n)	3(10.3%)	0(0%)	<0.01

A significantly increased frequency of family history of thyroid disease was reported in children with transient hypothyroidism (6.9% vs. 32.3%, $P = 0.03$). A reported positive history of hyperthyroidism occurred in 2 and 11 mothers of infants with permanent and transient hypothyroidism,

respectively. Iodine exposure occurred in 10% of infants with transient hypothyroidism. Iodine exposure and maternal autoimmune thyroid disease history was negative in 15transient hypothyroidism cases (Table 3).

Table 3. Maternal thyroid functional status and history of iodine exposure in permanent and transient hypothyroidism

Maternal thyroid function	Permanent hypothyroidism	Transient hypothyroidism	P-value
Hyperthyroidism	2	7	
Hypothyroidism	0	4	
History of Iodine exposure		4	
Total	2(6.9%)	11(26.2%)	0.03

4. Clinical manifestations

The common clinical findings in permanent hypothyroidism were prolonged jaundice (n=9, 31.0%), constipation (n=4, 13.8%), feeding problems (n=5, 17.2%), and delayed development (n=2, 6.9%). In the transient group, only three infants (18.7%) had prolonged jaundice that required phototherapy.

5. Thyroid function tests

Thyroid screening data is shown in Table 4. In infants with transient hypothyroidism, mean screening TSH (blood spot) was significantly lower than in those with permanent hypothyroidism (152.47 vs. 45.91 $p<0.01$) (Fig 1). Of the infants exceeding a TSH level of 39.0 uIU/ml, 8 had transient and 26 had permanent CH. With a cut-off value of 39.0IU/ml, sensitivity and specificity for permanent hypothyroidism is 93% and 67%,

respectively. The age at screening was no different between groups.

Fig 1. Mean TSH levels at neonatal screening and follow-up in permanent and transient hypothyroidism.

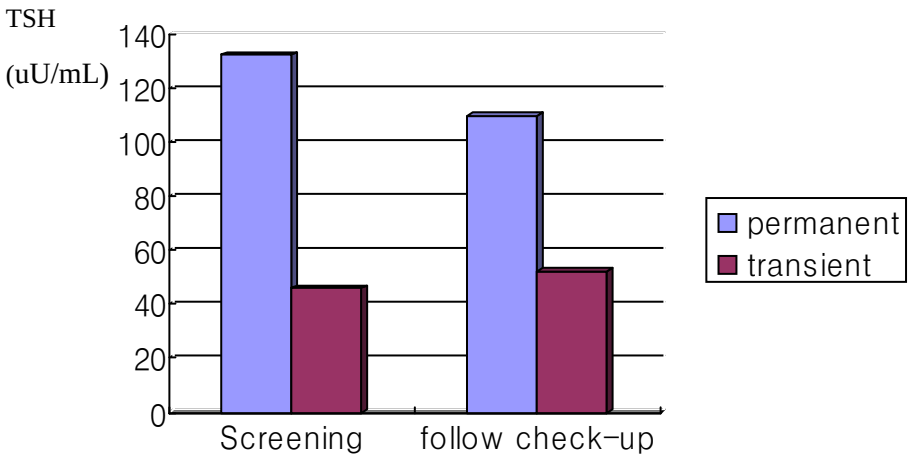

Table 4 shows thyroid function data upon follow-up. In transient hypothyroidism, TSH was significantly lower than in permanent hypothyroidism (110.07 vs. 52.43, $p<0.01$) (Fig 1). Mean free T4 levels were significantly lower in permanent hypothyroidism than in transient hypothyroidism (0.61 vs. 1.33, $p=0.04$). There was a significant difference in the mean T3 level between groups (95.03 vs. 157.35, $p<0.01$). In infants exceeding a TSH of 49.2 uIU/ml, 12 had transient and 27 had permanent hypothyroidism. With 49.2 uIU/ml as the cut-off value, the sensitivity and specificity of diagnosing permanent hypothyroidism are 97% and 61%, respectively. The age at screening was not different between the groups.

Table 4. Thyroid functional status in permanent and transient hypothyroidism.

	Permanent	Transient	P-value
Age at screening(days)*	3.11 ± 0.82	3.52 ± 0.61	NS
TSH at screening(uU/mL)	152.47 ± 108.32	45.91 ± 29.02	<0.01
Age at Follow check-up(days)*	23.42 ± 18.11	25.94 ± 15.63	NS
TSH at Repeat check-up (uU/mL)	110.07 ± 67.07	52.43 ± 39.02	<0.01
T3 at Repeat check-up(ng/dL)	95.03 ± 55.46	157.35 ± 53.85	0.04
fT4 at Repeat check-up(ng/dL)	0.61 ± 0.56	1.33 ± 0.48	0.04

*: median + SD

6. Thyroid function test after L-thyroxine medication

76 children in our study were diagnosed at an average age of 38 days. Table 5 shows thyroid function results following commencement of treatment. After an average period of 56.40±18.99 days, the 76 infants achieved a normal TSH. Infants with permanent hypothyroidism had a mean TSH significantly higher than those with transient hypothyroidism (8.21 vs. 3.75, p=0.34). Total T4 levels normalized in all groups after1.35 months. No statistical difference was found between groups for plasma T3 and free T4 levels.

Table 5. Thyroid functional status after L-thyroxine medication.

	Permanent	Transient	P-value
Duration of treatment(days)	63.12 ± 30.11	52.32 ± 20.11	NS
T3(ng/dL)	165.86 ± 49.54	176.14 ± 59.59	NS
fT4(ng/dL)	1.35 ± 0.54	1.27 ± 0.47	NS
TSH (uU/mL)	8.21 ± 12.55	3.75 ± 5,50	NS

Table 6 shows serial TSH levels between the two groups following treatment. Although normalization of mean TSH occurred after six weeks, mean TSH was lower in the transient hypothyroidism group than among those with permanent hypothyroidism.

Table 6. TSH values (uU/mL) during treatment.

	6weeks	3months	6months	12months	24months
Permanent hypothyroidism	9.54	7.21	5.43	4.81	2.5
Transient hypothyroidism	5.32	3.75	3,12	2.53	2.13

IV. DISCUSSION

It has been reported that the worldwide incidence of CH shows local differences (e.g. USA 1:4000, Japan 1:5000, Hong Kong 1:2404)[1,3,4]. Many authors have consistently reported lower prevalence in black subjects and higher prevalence in Asian and Hispanic subjects[5]. In Korea, CH prevalence varies from 1:4000-5000[6]. In our center, prevalence was found to be similar to previous reports.

CH can manifest as a permanent or transient condition. Permanent

dysfunction results from mal-development of the thyroid gland, whereas etiology of transient impairment is less clear and may include maternal factors, such as excessive iodine intake, anti-hyperthyroid medication, or the presence of auto-antibodies during pregnancy. Distribution of CH etiologies have been variously reported Fisher[1] described 63% dysgenesis, 23% ectopic thyroid, and 14% dyshormonogenesis, while Grant[7] reported 40% dysgenesis, 40% ectopic thyroid, and 6% dyshormomogenesis. Our findings were comparable to previous reports: 34% agenesis, 21% hypoplasia, 10% ectopic thyroid, and 34 % dyshormonogenesis.

Since the introduction of newborn screening, the detection rate of transient hypothyroidism has increased. Yang et al[8] reported transient hypothyroidism in 38% of cases. In Korea, 41.3% of CH infants were reported to have transient hypothyroidism[9]. In our study, we found that 43.1% of CH infants had transient hypothyroidism.

It is well established that hypothyroidism upon recall examination requires prompt L-thyroxine replacement therapy to avoid intellectual impairments. The American Academy of Pediatrics guidelines for children with suspected transient CH recommends a 30-day discontinuation of L-thyroxine after age three to evaluate the need for continuous therapy[10]. On the other hand, the European group recommends withdrawal of L-thyroxine at 18-24 months to abbreviate the duration of treatment and parental burden [11]. In a trial of early withdrawal of L-thyroxine, it was found that medication could be discontinued at around 0.7± 0.6 years old [12]. In our study, 25/42 patients (59.5%) with transient hypothyroid were treated with L-thyroxine for 1.84 ± 0.7 years 2 cases discontinued

medication at 3 and 6 months, respectively, and 15 cases were serially checked for thyroid function without medication and confirmed TSH normalization.

In CH cases with a normally located thyroid gland, it is difficult to differentiate between transient and permanent hypothyroidism before reevaluation. Previous studies have evaluated CH risk factors [13]. Our study confirmed higher prevalence of CH among females than males[14-17]. However, it is still unclear why females are more susceptible to developing permanent hypothyroidism. In addition, some authors have suggested prolonged gestation in infants with CH however only a few have presented data [18, 19]. On the other hand, it has been noted that transient hypothyroidism is frequent in prematurity and is possibly a result of transient immaturity of the gland with respect to hormone biosynthesis and adaptation external iodide supply[20]. In our study, no significant association was observed between gestational age and CH. As expected, a higher frequency of malformations has been observed among cases with permanent hypothyroidism (14.3%) [21-23]. In fact, the higher frequency of extrathyroidal congenital malformations observed supports the role of a common genetic component in the etiology of permanent hypothyroidismand at least some types of congenital defects.

Another important finding was the higher frequency of family history of hyperthyroidism or hypothyroidism observed among both permanent and transient hypothyroidism infants. It has been reported that maternal thyroid autoimmunity is not a frequent cause of permanent hypothyroidism, [24] but rather of transient hypothyroidism likely a

consequence of transplacental transfer of TSH receptor-blocking antibodies[25]. In our study, maternal thyroid disease history was frequently noted in cases of transient hypothyroidism.

As expected, cases of transient hypothyroidism had lower screening and follow-up TSH levels and higher fT4 levels. We attempted to use a cut-off value for distinguishing transient and permanent hypothyroidism; however limitation included only a small sample size. A larger study size would be needed.

We believe that, through multivariate factors, including female predominance, history of maternal thyroid disease, and TSH and fT4 levels, the distinction between transient and permanent CH could be made before the second year of life and that prolonged, unnecessary treatment could be avoided. However, as previously reported[26] and observed in our study, a slight rise in TSH can occur during serial follow-up, without medication or an early trial of discontinuing therapy. It should be remembered that subclinical hypothyroidism may be present later in life, even in those diagnosed with transient CH.

Germak et al.[27] and Hanokoglu et al.[28] found that infants with dyshormonogenesis had a more sensitive response to TSH suppression during treatment. Our study found that infants with dysgenensis and an ectopic thyroid showed significantly delayed normalization of TSH compared to the dyshormonogenesis group. This could be a reflection of a milder degree of hypothyroidism or an increased sensitivity of the hypothalamic-pituitary-thyroid axis in dyshormonogenesis to L-T4 therapy. Raza et al.[29] found that a delay in TSH normalization was not due to

pre-treatment with TSH, nor the etiology of CH. Other studies have showed etiology as the only independent factor affecting suppression of TSH and that pre-treatment thyroid function and plasma T4 levels do not affect suppression as previously thought. Therefore, CH etiology needs to be considered, as different treatment and follow-up schedules may be needed, with the goal of earlier thyroid function normalization.

Genetic involvement is suspected in CH, and previous studies have found gene anomaly involving *pax8* [30]. To date, no clear explanation has been found in humans, and further research will be needed.

V. CONCLUSION

A detailed phenotypic description of the various forms of neonatal hypothyroidism can enhance our understanding and management of CH. In particular, our results suggest multiple risk factors for permanent hypothyroidism, such as female sex, multiple defects, a high TSH level, and a low fT4 level, compared to male sex and maternal thyroid history for transient hypothyroidism. Although prevention of the neuropsychological consequences of CH using replacement therapy represents an important public health success, knowledge about modifiable risk factors could reduce the medication duration for infants affected by transient hypothyroidism.

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신생아 갑상선 선별검사상 이상을 보인 환아의 임상 경과

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이 순 민

선천성 갑상선 기능 저하증은 1/4000 의 빈도로 발생하며, 6주 이내에 치료를 시작하지 않으면 지능 저하와 신경학적 후유증을 나타내어 조기 진단 및 조기치료가 필수적인 질환이다. 본 연구는 2001년부터 2005년까지 세브란스 병원에서 출생한 신생아의 선천성 갑상선 기능 저하증의 빈도를 확인하고, 신생아 선별검사에서 이상을 보여 전원된 환아의 임상경과를 분석하여, 일과성 갑상선 기능저하증과 영구성 갑상선 기능저하증을 구분함으로써, 치료 기간을 단축할 수 있는 조기 진단 방법을 모색하고자 한다.

세브란스병원에서 출생한 신생아의 선천성 갑상선 기능저하증의 빈도는 1 /3,774이었다. 76명의 전원 된 환아에서 일과성 갑상선 기능저하증과 영구성 갑상선 기능저하증은 각각 42(55.3%)명과 29(38.2%)명이었으며, 영구성 갑상선 기능저하증의 원인은 무형성(n=10, 13.2%), 저형성(n=3, 3.9%), 이소성(n =6, 7.9%)과 호르몬 형성장애(n=10, 13.2%) 였으며, 갑상선 결합단백결핍은 5명이었다(n=5, 6.6%). 일과성 갑상선 기능저하증과 비교하여 여아의 빈도가 영구성 갑상선 기능저하증에서 유의하게 높았으며(1.54 vs. 0.55, P=0.015), 동반기형의 빈도도 영구성 갑상선 기능저하증에서 유의하게 높았다(10.3% vs.3.1%, P < 0.01). 모체의 갑상선 질환 가족력

은 일과성 갑상선 기능저하증에서 유의하게 높았다(6.9% vs. 32.3%, P = 0.03). 일과성 갑상선 기능저하증 환아에서 신생아 선별검사의 평균 TSH가 영구성 갑상선 기능저하증 환아에 비해 유의하게 낮았으며(152.47 vs. 45.91 p<0.01), 재검사한 TSH도 유의하게 낮았다(110.07 vs. 52.43, p<0.01). 평균 fT4는 영구성 갑상선 기능저하증 환아에서 일과성 갑상선 기능저하증 환아에 비해 유의하게 낮게 관찰되었다(0.61 vs. 1.33, p=0.04).

저자들은 여아, 동반 기형의 존재, 높은 TSH, 낮은 fT4가 영구성 갑상선 기능저하증을 예측할 수 있는 위험인자이며 남아, 모체의 갑상선질환 가족력, 낮은 TSH, 높은 fT4은 일과성 갑상선 기능저하증의 위험인자임을 확인하였다.

핵심되는 말 : 신생아 선별검사, 영구성 갑상선 기능 저하증, 일과성 갑상선 기능저하증