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Basal Serum Thyroxine Level should Guide Initial Thyroxine Replacement Dose in Neonates with Congenital Hypothyroidism

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What is already known on this topic?

High initial doses of sodium-levothyroxine (10-15 µg/kg/day) are recommended for rapid normalization of thyroid hormones and thyroid stimulating hormone, a marker of central nervous system hypothyroidism, for all infants with congenital hypothyroidism (CH).

What this study adds?

Our data suggest that standard high dose initial therapy in CH is not the only option. Adjusting the initial dose of thyroxine replacement to the basal serum free thyroxine level, with close follow-up in CH can be a valid strategy to provide target hormone levels while avoiding short-term iatrogenic hyperthyroxinemia.

Abstract

Objective: Initial high-dose sodium levothyroxine (Na-LT_4) (10-15 µg/kg/day) replacement for primary congenital hypothyroidism (CH) is recommended in guidelines. However, high-dose Na-LT_4 risks iatrogenic hyperthyroidism. The aim of this study was to investigate the normalizing effect of varying initial doses of Na-LT_4 on serum thyroid hormone levels.

Methods: Fifty-two patients were analyzed retrospectively. The patients were classified into mild (27/51.9%), moderate (11/21.1%) and severe (14/26.9%) CH, based on initial free thyroxine (fT_4) levels. Time taken to achieve target hormone levels was compared within groups.

Results: Initial mean Na-LT_4 doses for mild, moderate and severe disease were 6.9 ± 3.3, 9.4 ± 2.2 and 10.2 ± 2 µg/kg/day. Serum fT_4 levels reached the upper half of normal range (> 1.32 ng/dL) in a median of 16, 13 and 16 days in patients with mild, moderate and severe CH with the mean time from initial treatment to first control visit of 14.8 ± 6 days (range 1-36). There was no significant difference in terms of time to achieve target fT_4 hormone levels according to disease severity ($p = 0.478$). Seven (25.9%), eight (72.7%) and eight (57.1%) patients experienced hyperthyroxinemia (serum fT_4 > 1.94 ng/dL) in the mild, moderate, and severe CH groups at the first visit, respectively ($p = 0.016$).

Conclusion: Not all patients diagnosed with CH require high-dose Na-LT_4. Initial dose of Na-LT_4 may be selected on the basis of pre-treatment thyroid hormone levels. Some patients with moderate and severe CH, experienced iatrogenic hyperthyroxinemia even though the dose was close to the lower limit of the recommended range in guidelines. We suggest that lower initial doses may be appropriate with closer follow-up within the first week.

Keywords: Newborn screening, children, congenital hypothyroidism, Na-L thyroxine, dose

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Introduction

Congenital hypothyroidism (CH) is the most common endocrinological problem in newborns with an incidence of 1:2000-1:4000 and has a rising incidence, as reported in recent studies (1,2). Thyroid hormones are essential for brain development, especially prenatal neuronal differentiation, migration and proliferation, as well as postnatal myelinization. Thus a delay in diagnosis and treatment of permanent CH leads to irreversible brain damage and permanent neurodevelopmental defect (3,4).

Studies suggest that rapid normalization of thyroid hormones after birth, in infants with severe hypothyroidism may provide better cognitive outcomes (5). Therefore, guidelines for neonatal screening for CH recommend initial replacement doses of sodium levothyroxine (Na-LT_4) should be in the range 10-15 µg/kg/day to normalize serum thyroid hormone levels, and thus thyroid stimulating hormone (TSH) level, rapidly in order to achieve better outcomes (6). The guidelines also recommend the first follow-up visit should take place no more than 1-2 weeks after the initiation of Na-LT_4 treatment. However significant developmental improvement could not be shown for mild to moderate hypothyroidism using higher doses (7,8). Furthermore, recent data suggests a risk of iatrogenic hyperthyroxinemia may have a negative impact on behavior and attention in infants who are prescribed high initial doses (9,10,11). In light of this recent evidence, the latest European Society for Pediatric Endocrinology consensus guideline suggested, for the first time, that the initial dose of Na-LT_4 may be titrated with respect to initial hormone levels and disease severity (12).

In the current study, we aimed to investigate the effect of varying initial doses of Na-LT_4 on serum thyroid hormone levels in neonates and infants with primary CH.

Methods

Patients with primary neonatal CH diagnosed at Hacettepe University Medical Faculty, Division of Pediatric Endocrinology between January 2009 and January 2013 were included in the study. Patients, with a serum free thyroxine (fT_4) lower than 0.93 ng/dL (normal range: 0.93-1.71 ng/dL) and TSH higher than 10 mlU/L (normal range: 0.27-4.2 mIU/L) were considered to be primary CH. Patients with a gestational age of <37 weeks, history of severe underlying illness or central hypothyroidism, as well as those in whom treatment was delayed for three months were excluded from the study.

Patients' files were analyzed retrospectively to identify the etiology of CH and severity of hypothyroidism, as determined by initial fT_4 levels, as well as doses of Na-LT_4, and hormonal follow-up. Patients were grouped with respect to etiology, severity of CH, and initial dose of thyroxine (low vs high). Etiological classification of the study group relied on imaging as well as re-evaluation of thyroid hormones at three years of age after cessation of treatment.

Groups

(i) Patients were categorized into two groups: (a) patients with normal thyroid function after therapy withdrawal at three years of age were classified as transient CH; (b) patients with persistent hypothyroidism following cessation of therapy at three years of age were considered to have permanent CH. Both groups were compared for the time to achieve target hormone levels from onset of treatment.

(ii) Patients were categorized into three groups according to pretreatment plasma fT_4 concentrations: severe CH (fT_4 ≤0.31 ng/dL); moderate CH (0.31 < fT_4 ≤ 0.62 ng/dL) and mild CH (fT_4 > 0.62 < 0.93 ng/dL). Mild, moderate and severe CH groups were compared for the time to reach target hormone levels from onset of treatment.

(iii) Patients were divided into two groups with respect to initial dose of Na-LT_4. Those with an initial dose less than 10 µg/kg/day were defined as the low-dose group and those with an initial dose more than 10 µg/kg/day were defined as high-dose group. Both groups were compared for the time to achieve target hormone levels from onset of treatment.

Hormone Levels

Initial and follow-up thyroid hormone levels were extracted from medical records to analyze time to reach euthyroidism. Treatment targets were: (1) to achieve upper half of normal range for serum fT_4 (>1.32 ng/dL); and (2) serum TSH <10 mIU/L. In most patients, records included serum fT_4 and TSH levels every 1-2 weeks for the first two months of life, then every 1-3 months until 12 months of age, and thereafter every three months; and more often in those with problems with compliance during follow-up, though due to the retrospective nature of the study the time intervals between visits were not homogeneous. Blood samples were obtained in the morning before Na-LT_4 administration.

Patients who experienced a serum fT_4 level lower than 0.93 ng/dL at the first visit were considered to be hypothyroid.

Dose management of Na-LT_4 was made on an individual basis by the primary endocrinologist. However, the general approach in our department is to adjust the initial dose to pretreatment fT_4 levels.

This was a retrospective analysis of medical records. Serum fT_4 and TSH levels were measured by chemiluminescence method using IMMULITE 2000 System (Siemens, UK) during the studied period. Intra- and inter-assay variation coefficients for TSH were 5.3% and <6.4% and <7.1% and <7.8% for fT_4, respectively.

Iatrogenic Hyperthyroxinemia

Serum fT_4 levels higher than 1.94 ng/dL in the first visit among transient/permanent CH, mild/moderate/severe CH, and low-dose/ high-dose initial therapy groups were analyzed.

This study was approved by Hacettepe University Medical Faculty Non-Invasive Clinical Research Ethics Committee (GO 13/406-24).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 22.0 software (IBM Inc., Chicago, IL, USA). Numerical variables were summarized by mean ± standard deviation or median (minimum-maximum) as appropriate. Normality of the numerical variables was assessed with the Shapiro-Wilks test. As all numerical data sets had skewed distribution, nonparametric tests including Kruskal-Wallis and Mann-Whitney U test were used to compare independent groups (such as CH groups). Differences between groups in terms of categorical variables were examined by the chi-square test or Fisher's exact test. A p value less than 0.05 was considered statistically significant.

Results

Seventy-one patients with CH were extracted from hospital records within the time frame. Of these, seven patients were excluded since the age at diagnosis was later than 45 days and eight patients were excluded for non-compliance leading to treatment failure to reach target serum levels. Furthermore, four patients with subclinical hypothyroidism with unknown cause (etiology was unknown at diagnosis, and serum fT_4 were normal, however TSH levels were elevated after cessation of treatment at three years of age) were also excluded. Thus the final study group consisted of 52 children. Twenty-three (44.2%) were girls and 29 (55.5%) were boys. Mean age at diagnosis and treatment was 20.6 ± 9.9 days (7-43). Consanguinity was present in 28.8% of the parents.

Twenty-three (44.2%) patients had spot urinary iodine measurements, none of the results showed exposure to excessive iodine. Twenty-one (40.4%) mothers had spot urinary iodine measurements, which showed iodine sufficiency in four (19%) and deficiency in 17 (91%). Seven (41.2%) had mild (5-10 µg/dL), seven (41.2%) moderate (2-5 µg/dL) and three (17.6%) severe (<2 µg/dL) iodine deficiency. Babies of ten mothers with iodine deficiency (58.8%) were in the transient CH group, whereas the remaining seven (41.2%) were in the permanent CH group.

Mean serum levels of fT_4 and TSH at diagnosis were 0.75 ± 0.48 ng/dL and 70.6 ± 48.8 mIU/L, respectively. Mean initial Na-LT_4 dose was 8.4 ± 3.1 µg/kg/day. The mean time from initial treatment to first control visit was 14.8 ± 6 days (1-36).

The median time for fT_4 level to rise above 1.32 ng/dL was 16 (1-100) days, and the median time for TSH level to go below 10 mIU/L was 17 (1-88) days.

None of the patients experienced hypothyroidism at the first visit; 48 patients (92.3%) achieved target serum fT_4 levels and only four children (7.7%) had fT_4 levels in the lower half of the normal range (0.99-1.31 ng/dL). Three of these four had achieved target serum fT_4 levels by the second visit (12-31 days); one had initial low-dose Na-LT_4 (7.14 µg/kg/day) and the other two had initial high-dose Na-LT_4 (10.53 and 12.2 µg/kg/day). The remaining one achieved target serum fT_4 levels by the third visit (100th day), he had initial low-dose Na-LT_4 (7.35 µg/kg/day).

Disease Severity

Twenty-seven (51.9%) patients had mild, 11 (21.1%) moderate, and 14 (26.9%) severe CH. The mean initial Na-LT_4 dose given to mild, moderate and severe groups were 6.9 ± 3.3, 9.4 ± 2.2 and 10.2 ± 2 µg/kg/day, respectively. The initial treatment dose of the mild group was significantly lower than that of moderate and severe groups ($p < 0.001$). High-dose initial Na-LT_4 treatment was initiated in four (14.8%), six (56.5%) and eight (57.1%) patients in the mild, moderate and severe groups, respectively ($p = 0.006$).

The median time for patients to reach target serum levels of fT_4 (>1.32 ng/dL) was 16 (3-49), 13 (7-100) and 16 (1-36) days for mild, moderate and severe groups, respectively ($p = 0.478$). The median time for patients to achieve target serum TSH levels (<10 mIU/L) was 16 (5-31), 15 (8-27) and 30 (1-88) days in the mild, moderate and severe groups, respectively ($p = 0.003$).

Permanent versus Transient Congenital Hypothyroidism

Twenty-four (46.1%) patients had permanent CH, and 28 (53.9%) had transient CH. In the permanent CH group, 13 patients had dysgenesis and 11 had dyshormonogenesis. Of 13 patients with thyroid dysgenesis, three (23.1%) had

agenesis, eight (61.5%) had ectopy, with one case (7.7%) each of hypoplasia and hemiagenesis.

The mean initial Na-LT_4 dose was 9.8 ± 2.8 and 7.1 ± 2.9 µg/kg/day in patients with permanent and transient CH, respectively with the initial dose being significantly higher in patients with permanent CH (p = 0.003) (Table 1). Twelve patients (50%) in the permanent, and six patients (21.4%) in the transient CH group underwent high-dose initial Na-LT_4 therapy (p = 0.031).

Thirteen (54.2%), seven (29.2%) and four patients (16.7%) with severe, moderate and mild CH, respectively, were in the permanent CH group. In contrast in the transient group there was one (3.6%) child with severe CH, and four (14.3%) and 23 (82.1%) children with moderate and mild CH, respectively, based on pre-treatment fT_4 concentration. While the patients with severe CH were mainly in the permanent group, the patients with mild CH were principally in the transient group (p < 0.001).

The median time for serum levels of fT_4 to rise above 1.32 ng/dL was 15.5 (1-49) and 16 (3-100) days in patients with permanent and transient CH, respectively (p = 0.927). The median time for serum levels of TSH to decrease below 10 mIU/L was 18.5 (1-88) and 16 (5-31) days in patients with permanent and transient CH, respectively (p = 0.079). No statistically significant difference was found between the two groups.

Low versus High Initial Dose of Na-LT_4

The mean initial Na-LT_4 dose was 11.8 ± 1.4 µg/kg/day for the patients in the high dose group (n = 18, 34.6%) and 6.4 ± 2.1 µg/kg/day for the low dose group (n = 34, 65.4%) (Table 2).

The median time for fT_4 level to increase above 1.32 ng/dL was 12.5 (1-49) days for patients in the high-dose, and 16 (3-100) days for patients in the low-dose group (p = 0.081). The median time for TSH level to decrease below 10 mIU/L was 17 (1-83) days for patients in the high-dose, and 17 (5-88) days for patients in the low-dose group (p = 0.664). No statistically significant difference was found between the groups.

Overtreatment

Analysis of fT_4 levels revealed that 23 (44.2%) patients experienced serum levels of fT_4 > 1.94 ng/dL at the first visit. None of them showed any signs/symptoms of hyperthyroidism.

The effect of high initial doses on fT_4 at the first visit were compared. The mean time from initial treatment visit to first follow-up visit was 11.7 ± 5.1 and 16.4 ± 6 days in the high-dose, and low-dose treatment groups, respectively (p = 0.005). We compared high-dose, and low-dose initial treatment in terms of iatrogenic hyperthyroxinemia during the course of reaching treatment goals; 10 (55.5%) and 13 (38.2%) patients experienced serum levels of fT_4 > 1.94 ng/dL in the high-dose and low-dose treatment groups at the first visit, respectively (p = 0.36).

Mild, moderate and severe CH groups were also compared in terms of iatrogenic hyperthyroxinemia at the first visit. The mean time from initial treatment visit to first follow-up visit was 14.9 ± 7.7, 13.4 ± 5.8 and 15.3 ± 5.3 days in mild, moderate, and severe CH groups, respectively (p = 0.33). Seven (25.9%), eight (72.7%) and eight (57.1%) patients experienced serum levels of fT_4 > 1.94 ng/dL in mild, moderate, and severe CH groups at the first visit, respectively (p = 0.016)

Finally, permanent and transient CH groups were compared in terms of iatrogenic hyperthyroxinemia at the first visit. The mean time from initial treatment visit to first follow-up visit was 14.5 ± 6.6 and 15.1 ± 5.1 days in permanent and transient groups, respectively (p = 0.47). Fifteen (62.5%) and eight (28.6%) patients experienced serum levels of fT_4 > 1.94 ng/dL in the permanent and transient CH groups at the first visit, respectively (p = 0.03).

Table 1. Pretreatment serum fT_4 and thyroid stimulating hormone (TSH) levels, initial Na-LT_4 doses and days to achieve target serum fT_4 and TSH levels in permanent and transient congenital hypothyroidism groups

		Initial levels			Time to achieve target hormone levels (days)	
		fT_4*	TSH*	Dose*	fT_4**	TSH**
Etiology	N	(ng/dL)	(mIU/L)	(µg/kg/day)	> 1.32 ng/dL	< 10 mIU/L
Permanent	24	0.4 ± 0.29	95.1 ± 51.7	9.8 ± 2.8	15.5	18.5
Transient	28	1.05 ± 0.4	49.6 ± 35.1	7.1 ± 2.9	16	16
p		< 0.001	< 0.001	0.003	0.927	0.079

*Mean ± standard deviation, **median.
TSH: thyroid stimulating hormone, fT_4: free thyroxine, Na-LT_4: sodium levothyroxine

Table 2. Pretreatment serum fT_4 and thyroid stimulating hormone (TSH) levels, initial Na-LT_4 doses and days to achieve targeted serum fT_4 and TSH levels in high and low-dose groups

		Initial levels			Time to achieve target hormone levels (days)	
		fT_4*	TSH*	Dose*	fT_4**	TSH**
Dose	N	(ng/dL)	(mIU/L)	(µg/kg/day)	> 1.32 ng/dL	< 10 mIU/L
High	18	0.44 ± 0.27	102.1 ± 54.7	11.8 ± 1.4	12.5	17
Low	34	0.94 ± 0.49	53.9 ± 36.2	6.4 ± 2.1	16	17
p		0.001	< 0.001	< 0.001	0.081	0.664

*Mean ± standard deviation, **median.
TSH: thyroid stimulating hormone, fT_4: free thyroxine, Na-LT_4: sodium levothyroxine

Discussion

CH is one of the most common treatable causes of intellectual disability. Studies have shown that thyroid hormones have a crucial role in the appropriate formation of neuronal architecture as well as differentiation (13,14). High initial doses of Na-LT_4 (10-15 µg/kg/day) are recommended for rapid normalization of thyroid hormones and TSH for all infants, irrespective of severity and cause of CH. There are studies that have shown lower doses may also have similar success with less risk of overtreatment (6,9,15,16). Supraphysiological levels of fT_4 may result in premature craniosynostosis, behavioral problems, and attention impairment, and furthermore, may have a negative effect on IQ at adolescence, as one Dutch study has shown (15,16,17,18). Although the importance of early detection and effective treatment of CH is beyond dispute, there are some controversies in standard high dose Na-LT_4 (19,20).

Soliman et al (21) reported that around one quarter of 45 patients who received high dose Na-LT_4 (15 µg/kg/ day) as initial therapy experienced hyperthyroxinemia during follow-up. Craven and Frank (9) showed high initial Na-LT_4 (> 12.5 µg/kg/day) may lead to hyperthyroxinemia that required dose reduction in more than half of the patients during follow-up. They suggested a narrower range for dosing would avoid over-treatment. Furthermore, limited information is available about how a targeted dosing strategy compares to initial high dosing (10-15 µg/kg/day) to achieve target serum fT_4 and TSH levels. We aimed to provide some data on this issue, and we have evaluated patients diagnosed with primary CH and investigated the influence of different initial doses of Na-LT_4 on thyroid hormone levels as well as the time to achieve target levels. We also analyzed the time to achieve target hormone levels from onset of treatment in perspective of etiologies and disease severity. Furthermore, we analyzed patients who developed hyperthyroxinemia during initial hormone treatment, and its relation to initial doses, disease severity and whether CH was permanent or transient.

Mathai et al (22) has questioned single initial Na-LT_4 dose for all CH patients and reviewed variable initial dose strategy in permanent CH. In their study, Na-LT_4 treatment was given in 10, 12 and 15 µg/kg/day doses for dyshormonogenesis, ectopia and athyreosis, respectively. They showed these doses succeeded in normalizing serum fT_4 within 14 days. They also showed that lower doses (9.98 ± 3.19 µg/kg/day) of Na-LT_4 enabled target serum fT_4 levels in cases with permanent CH within a median of 16 days. Bakker et al (23) studied 30 CH neonates who were treated with initial daily T_4 dosages ranging from 4.8 to 11.1 µg/kg and found no correlation between the initial dose (whether high or low) and the time for normalization of plasma fT_4 levels. The mean initial Na-LT_4 dose was 8.4 ± 3.1 µg/kg/day in the current study, moreover both low (6.4 ± 2.1 µg/kg/day) and high (11.8 ± 1.4 µg/kg/day) dose groups achieved target serum fT_4 and TSH levels within similar time frames. Tuhan et al (24) studied the effect of three different initial Na-LT_4 doses (6-9.9 µg/kg/day, 10-11.9 µg/kg/day and 12-17 µg/kg/day) on serum TSH levels in the first month, and reported no statistical difference between groups.

In the current study, varying initial doses of Na-LT_4 (6.9 ± 3.3; 9.4 ± 2.2; 10.2 ± 2 µg/kg/day) in mild, moderate, and severe CH groups achieved target fT_4 serum concentrations within similar time-frames, suggesting titration of initial Na-LT_4 doses to initial hormone levels may be a valid strategy for effective treatment. We showed comparable efficacy of lower doses to achieve target serum fT_4 levels in the mildly and moderately affected subgroups, against severe hypothyroidism treated with high doses. However, it took longer for the severe CH group to achieve target TSH serum concentrations than the mild and moderate groups (30 vs 16,15 days respectively) in our study. Persistent high serum levels of TSH in early phase of treatment has been reported. Furthermore fT_4 concentration is considered more helpful in determining T_4 supplementation doses in this specific time span in some studies (23,25). Our results suggest impairment of hypothalamic-pituitary-thyroid axis negative feedback control may be more pronounced in the severe CH

subgroup, as has previously been suggested by Hanukoglu et al (26).

Our cohort has an increased percentage of transient CH (53.9%), similar to the recently published French study in which more than half of the study population had transient CH (27). The increased percentage of transient CH in these studies may be attributed to iodine deficiency in both countries (27,28). Spot urinary iodine measurements of the mothers in the current study also showed that iodine deficiency is still a problem in the maternal age group. A good number of patients in both our cohort and French study presented with mild hypothyroidism at the time of diagnosis and received lower initial doses of Na-LT_4 in comparison to guidelines. We consider this special subgroup of patients with mild, and usually transient, hypothyroidism may be related to iodine deficiency rather than primary congenital defects of the thyroid gland or hormonogenesis, and they may need lower initial Na-LT_4 replacement doses. Furthermore, they may have an increased risk of overtreatment with standard high dose therapy.

Hyperthyroidism is an issue in high-dose treatment. Tuhan et al (24) studied 71 children with CH, and showed 43.1% of patients were overtreated. Furthermore, five of them experienced clinical signs of hyperthyroidism but initial follow-up in this study was delayed. They suggested following-up thyroid functions earlier than 30 days. Mathai et al (22) monitored thyroid functions weekly and reported 28% of their patients had supraphysiological fT_4 levels within the first month of treatment. Their data suggests close monitoring during the early follow-up may decrease risk of overtreatment. The mean time from initial treatment to first control visit was 14.8 ± 6 days in our study, and 23 (44.2%) of the infants experienced iatrogenic hyperthyroxinemia due to overtreatment at the first visit.

Lower doses titrated to initial hormone levels were preferred in the current study, rather than the high-doses recommended in the guidelines. Yet some patients still experienced hyperthyroxinemia. Thus these results support closer follow-up, especially in patients with higher initial doses.

Study Limitations

The current study has some constraints, such as its retrospective nature and the small number of cases. In addition, neither the doses nor follow-up schedule were predetermined. Rather, they were decided by the primary endocrinologists, and time to target range of hormones depended on the follow-up schedule so that the exact timing is unknown. A limited number of babies and mothers had urinary spot urinary iodine measurements. Furthermore, anthropometric parameters and data regarding long-term neuropsychological outcome are not available.

Conclusion

Our data adds to the growing number of studies suggesting that standard high dose initial therapy needs to be reconsidered in CH. This may be especially true for areas where mild transient CH is endemic due to iodine deficiency or frequent follow-up in the first weeks of treatment is not practical. We suggest that basal serum fT_4 level may guide the initial dose of thyroxine replacement in neonates suspected of having CH, and, where possible, more frequent follow-up should be employed for dose adjustment in the first weeks, in order to prevent overtreatment. Long-term studies are necessary to determine the validity of such treatment, and whether it has any impact on the neurocognitive outcomes of children with CH.

Ethics

Ethics Committee Approval: This study was approved by Hacettepe University Medical Faculty Non-Invasive Clinical Research Ethics Committee (GO 13/406-24).

Informed Consent: Due to the retrospective nature of the study, patient consent was waived.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ceren Günbey, Alev Özön, E. Nazlı Gönç, Ayfer Alikaşifoğlu, Nurgün Kandemir, Concept: Ceren Günbey, Alev Özön, Data Collection or Processing: Ceren Günbey, Alev Özön, Analysis or Interpretation: Ceren Günbey, Alev Özön, E. Nazlı Gönç, Ayfer Alikaşifoğlu, Sevilay Karahan, Nurgün Kandemir, Literature Search: Ceren Günbey, Alev Özön, Writing: Ceren Günbey.

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