

Thyroid Functions in Children with Cerebral Palsy and Effects of Phenobarbital on Thyroid Hormones

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Abstract

Thyroid function tests were performed on 44 patients with cerebral palsy (CP) and on 35 healthy children as the control group. In the patient group total triiodothyronin (TT₃), total thyroxine (TT₄), free triiodothyronin (FT₃), free thyroxine (FT₄) and thyroid-stimulating hormone (TSH) levels were found in wholly normal ranges. These values have shown no significant difference with respect to those of the control group ($p>0.05$). It was striking that 43 %, 41 % and 55 % of the patients were under 3 percentile according to length, weight and head circumference respectively. Thyroid function tests of the patients with growth retardation had no significant difference from those of the controls and patients without growth retardation. The TT₄ and FT₄ levels in the patients using phenobarbital were considerably lower than those that are not using it ($p<0.05$). However, there were no significant difference in two groups with respect to T₃ and TSH levels.

Key Words: Cerebral palsy, thyroid function, phenobarbital.

Serebral Palsi'li Hastalarda Tiroid Fonksiyonları ve Bu Hastalarda Phenobarbitalin Tiroid Hormonlarına Etkisi

Özet

Serebral palsi'li 44 hastada tiroid fonksiyon testleri tayin edildi. Kontrol grubu olarak 35 sağlam çocuk seçildi. Hasta grubunda T₃, T₄ ve TSH seviyeleri normal sınırlarda olup, kontrol grubuna göre aradaki fark istatistiksel olarak önemsizdi ($p>0.05$). Serebral palsi'li hastaların % 43'ü boyca, % 41'i ağırlıkça, % 55'i baş çevresi bakımından 3 persentilin altındaydı. Gelişme geriliği olan hastalarda tiroid fonksiyon testleri kontrol grubuna göre önemli bir farklılık göstermedi ($p>0.05$). Antikonvülzan olarak phenobarbital alan hastalarda TT₄ ve FT₄ değerleri ilaç almayanlara göre anlamlı olarak düşüktü ($p<0.05$).

Anahtar Kelimeler: Serebral palsi, tiroid fonksiyonları, phenobarbital.

Cerebral palsy (CP) is not a specific disease or syndrome. It comprises a group of motor disorders characterized by abnormal control of movement or posture present from birth. The dysfunction is caused by brain impairment and is neither episodic nor progressive (1-3).

CP is the most common movement disorder of childhood. It's prevalence has been reported to be about 1.2 to 2.3 per 1000 by early school age (1,2,4).

The cause is often obscure or multifactorial. Intrauterine hypoxia is a frequent cause (3,5-7). Nevertheless, the causes of CP in the vast majority of patients are unknown (1,3).

It is characterized by paralysis, weakness, incoordination or ataxia. Of these patients with CP, approximately 25 % to 50 % have some type of seizure disorder (2,5,9), 50 % to 70 % have mental retardation (2,10).

Thyroid hormone (TH) has both general and specific effects on growth. An important effect of TH is to promote growth and to develop the brain during fetal and for the first few years of postnatal life (11).

The purpose of the present study was an evaluation of the growth status of the patients with CP, and an investigation of the thyroid hormone levels, and determination of the effect

on thyroid function of long-term anticonvulsant treatment with phenobarbital in the same patients.

Patients and Methods

This study was carried out using 44 patients with CP registered to the Rehabilitation Center for Turkish Spastic Children's Society in Isparta. Thirty five healthy children that were admitted to our out-patient clinic, were selected as the control group. The children that were diagnosed previously as CP were reexamined by the pediatricians and neurologists. The earlier diagnosis was confirmed by physical and neurological examinations, and laboratory findings. According to the Neyzi's Growth Chart, patients were divided into three groups, as under 3, 3 to 50, and 50 to 97 percentiles for length, weight and head circumference (12). From the patients, those who are regularly using phenobarbital for at least a year were selected. Thirteen of these patients who are using phenobarbital were identified.

Venous blood samples were taken from all of the patients and stored at the -20°C until analysis. Total triiodothyronin (TT_3), total thyroxine (FT_4), free triiodothyronin (FT_3), free thyroxine (FT_4) and thyroid-stimulating hormone (TSH) levels of blood samples were determined with enzyme linked fluorescent assay (ELFA) by using VIDAS device of BioMerieux™ Company. The patient and the control groups, and drug administered patient and no drug administered patient groups were compared with each other with respect to thyroid hormone (TH) levels.

The results were evaluated statistically by using a statistics software package, namely Microstat. All data were expressed as mean \pm SD. Statistical analysis of comparisons between different groups was done using Student's t-test. P value <0.05 was considered significant.

Results

The ages of the CP patients were between 1 to 14 years and 18 of them were girls and the rest (26) were boys. The ages of the control group were ranging from 2 to 13, and 15 of them were girls and 20 of them were boys. The age and sex distribution of the patient and control groups were shown in Table 1.

CP patients were divided into three groups with respect to the percentile values of length,

weight and head circumference measurements. In this distribution, less than 3, 3 to 50, and 50 to 97 percentile ranges were taken into consideration. There was no patient who had a greater value than 97 percentile.

Table 1. The distribution of the cases according to the age and sex in patient and control groups.

| Ages (year) | Patient Group | | | Control Group | | |
|-------------|---------------|------|-------|---------------|------|-------|
| | Girls | Boys | Total | Girls | Boys | Total |
| 1-3 | 3 | 6 | 9 | 2 | 3 | 5 |
| 4-6 | 8 | 12 | 20 | 8 | 9 | 17 |
| 7-14 | 7 | 8 | 15 | 5 | 8 | 13 |
| Total | 18 | 26 | 44 | 15 | 20 | 35 |

Table 2 shows the length, weight and head circumference percentile values for boys and girls separately. Of the whole patient group, 19, 18, and 21 patients were under 3 percentile according to length, weight, and head circumference respectively.

However, all of the patients had normal TH levels (Table 3), and also there was no significant difference between the control and the patient groups ($p>0.05$).

The serum thyroid hormones in CP according to the percentiles for length, weight and head circumference are shown in Table 4. Only the groups less than 3 and 3 to 50 were taken into consideration for TH evaluation, and the 50 to 97 percentile group was discarded because of inadequate number of patients. The TH levels of the two group were in normal ranges, and there were no significant difference between two groups ($p>0.05$).

Table 2. The distribution of girl and boy cases according to the percentile values for length, weight, and head circumference.

| | Percentiles for girls | | | Percentiles for boys | | |
|----|-----------------------|------|-------|----------------------|------|-------|
| | <3 | 3-50 | 50-97 | <3 | 3-50 | 50-97 |
| L | 9 | 8 | 1 | 10 | 13 | 3 |
| W | 7 | 8 | 3 | 11 | 10 | 5 |
| HC | 11 | 5 | 2 | 13 | 9 | 4 |

L: Length W: Weight HC: Head Circumference

Table 5 shows the TH levels of the patient groups using drugs. The obtained values were compared with those of the control and no drug using patients. It was found that among all the hormone levels, only TT_4 and FT_4 levels of the patients using phenobarbital were significantly less than that of the control group.

Table 3. Serum thyroid hormones in patients and control subjects (mean± SD).

| Group | TT ₃ (0.95-2.50) nmol/ml | FT ₃ (4.00-8.35) pmol/L | TT ₄ (60-120) nmol/L | FT ₄ (9-20) pmol/L | TSH (0.25-5.00) µ IU/ml |
|----------|--|---------------------------------------|------------------------------------|----------------------------------|----------------------------|
| CP | 1.92±0.36 | 6.22±0.48 | 97.43±5.52 | 16.61±2.45 | 3.28±1.23 |
| Control | 2.08±0.35 | 7.01±0.67 | 102.24±3.43 | 17.65±1.97 | 3.36±0.98 |
| p values | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 |

Table 4. Serum thyroid hormones in CP according to the percentiles for length, weight and head circumference.

| Percentiles | Measurement | TT ₃ | FT ₃ | TT ₄ | FT ₄ | TSH |
|-------------|-------------|-----------------|-----------------|-----------------|-----------------|-----------|
| <3 | Length n=19 | 1.62±0.67 | 5.77±1.87 | 94.61±2.45 | 16.48±3.20 | 3.21±0.65 |
| | Weight n=18 | 2.18±0.27 | 6.36±0.42 | 96.79±3.24 | 17.08±2.41 | 4.12±0.95 |
| | HC n=19 | 2.14±0.36 | 6.13±0.23 | 89.95±4.72 | 17.13±2.25 | 4.53±1.34 |
| 3-50 | Length n=21 | 1.97±0.70 | 6.11±1.08 | 98.56±3.15 | 17.76±2.21 | 3.71±0.46 |
| | Weight n=18 | 2.07±0.40 | 6.76±1.54 | 102.79±3.63 | 16.78±2.35 | 3.62±0.64 |
| | HC n=16 | 2.14±0.26 | 6.63±1.37 | 99.25±4.68 | 17.53±2.19 | 4.13±1.33 |

n= number of subjects

Table 5. Thyroid hormone levels of drug administered and non administered groups.

| Group | TT ₃ (nmol/ml) | FT ₃ (pmol/L) | TT ₄ (mol/L) | FT ₄ (pmol/L) | TSH (µ IU/ml) |
|--------------------|---------------------------|--------------------------|-------------------------|--------------------------|---------------|
| Phenobarbital n=13 | 2.01±0.43 | 6.96±1.94 | 79.14±4.66 | 11.92±2.24 | 3.52±0.75 |
| No drug n=31 | 2.11±0.38 | 7.54±0.49 | 108.87±7.53 | 18.01±1.48 | 3.38±1.53 |
| P value | >0.05 | >0.05 | <0.05 | <0.05 | >0.05 |

n= number of subject

Discussion

Although the defining disability of CP is motor disfunction, several other type of disabilities are also present. Even though CP is a static encephalopathy, effects of the central lesions are changeable with age (13).

In the present study the boys to girls ratio of the patients were 1.44 which is in conformity with 1.5 value reported in the literature. The highest number of patients were in the 4 to 6 age group. Table 3 shows that the length and head circumference growth of girls were less than that of boys. In the CP diagnosis, a common indication is that the head circumference value was under 3 percentile (10).

An obvious growth retardation was seen in the patient group, a finding which requires to be paid attention to. To determine whether thyroid hormones effect this growth retardation, several hormonal investigations were carried out. According to our results all of the TH levels were normal in the patient group, and there were no significant difference between the patients and the control groups. We are not able to compare this results with the others, because we couldn't find any earlier study related to this subject in the literature. In conclusion our results indicate that the growth retardation in patients with CP was not due to secondary thyroid hormonal changes, leaving us with an important question what causes the growth retardation in patients with CP. It can be speculated that growth retardation in patient with CP may be due to primary cerebral

injury or other endocrine disorders that come into being secondary cerebral injury or the other factors such as nutritional deficiency.

It was reported that some of the drugs used for treatment affect the endocrine system (14-16). According to our study it was found that although all of the TH levels of phenobarbital using patients were in normal ranges, only TT₄ and FT₄ levels were significantly lower than that of the no drug administered group ($p < 0.05$). This finding of our study is in agreement with statement that phenobarbital induced function oxidases and enhance clearance of thyroxine. This effect may be accompanied by increased T₄ to T₃ conversion. This drug decreased TT₄ and FT₄ with normal T₃ and TSH due to combined effects (16-19). This result is in conformity with findings of other investigators (18, 20-22). There are some reports indicating that anticonvulsants not only affect thyroid hormones subclinically, but also cause clinical hypothyroidism (23). For this reason thyroid functions must be monitored in patients receiving anticonvulsant therapy.

References

- 1-Ashwal S, Swaiman KF. Developmental abnormalities of the central nervous system. In: Joynt RJ, editor. *Clinical Neurology*. Vol.4. Philadelphia: JB Lippincott, 1992; 1-84.
- 2-Nelson KB. Cerebral palsy. In: Swaiman KF, editor. *Pediatric Neurology, Principles and Practice*. Vol.1. St. Louis: CV Mosby, 1989; 363-71.
- 3-Huttenlocher PR. The nervous system. In: Behrman RB, Vaughan VC, Nelson WE, editors. *Textbook of Pediatrics*. Philadelphia: WB Saunders, 1987; 1274-330.
- 4-Shapiro BK, Capute AJ. Cerebral palsy. In: Oski FA, Deangelis CD, Feigin RD, McMillan JA, Warshaw JB, editors. *Principles and Practice of Pediatrics*. Philadelphia: JB Lippincott, 1994; 679-86.
- 5-Moe PG, Seay AR. Neurologic, Muscular Disorder. In: Hathaway WE, Hay WW, Groothuis JR, Paisley JW, editors. *Current Pediatric Diagnosis and Treatment*. Beirut: Middle East Edition, 1993; 674-747.
- 6-Freeman JM, Nelson BL. Intrapartum asphyxia and cerebral palsy. *Pediatrics* 1988; 82: 240-3.
- 7-Paneth N. The causes of cerebral palsy. Recent evidence. *Clin Invest Med* 1993; 16 (2): 95-102.
- 8-Stanley FJ. The aetiology of cerebral palsy. *Early Hum Dev* 1994; 36 (2): 81-8.
- 9-Murphy CC, Yeargin A, Lsopp M, Decoufle P, Drews CD. Prevalence of cerebral palsy among ten-year-old children in metropolitan Atlanta, 1985 through 1987. *J Pediatr* 1993; 123 (5): 13-20.
- 10-Yalaz K. Serebral palsi. Renda Y, Yalaz K, Özdirim E, Aysun S. editörler. *Pediatric Nöroloji*. Ankara: Türkiye Sağlık ve Tedavi Vakfı yayın no: 2, 1983; 89-98.
- 11-Guyton AC. *Textbook of Medical Physiology*. Philadelphia: WB Saunders, 1991; 831-41.
- 12-Neyzi O. Büyüme ve Gelişme. Neyzi O, Ertuğrul T. editörler. *Pediatric*. İstanbul: Nobel Tıp Kitabevi, 1993; 69-114.
- 13-Percy AK. Static encephalopathy. In: Oski FA, Deangelis CD, Feigin RD, McMillan JA, Warshaw JB, editors. *Principles and Practice of Pediatrics*. Philadelphia: JB Lippincott, 1994; 2025-28.
- 14-Luhdorf K. Endocrin function and antiepileptic treatment. *Acta Neurol Scand* 1983; 67: 15-20.
- 15-Gallagher BB, Baumel IP, Mattsa RH, Woodbury SG. Pyrimidon, diphenylhydantoin and phenobarbital. Aspects of acute and chronic toxicity. *Neurology* 1973; 23: 145.
- 16-Isojarvi JIT, Pakarinen AJ, Ylipalossari PJ. Serum hormones in male epileptic patients receiving anticonvulsant medication. *Arch. Neurol* 1990; 47: 470-6.
- 17-Donohoue PA. The Thyroid Gland. In: Oski FA, Deangelis CD, Feigin RD, McMillan JA, Warshaw JB, editors. *Principles and Practice of Pediatrics*. Philadelphia: JB Lippincott, 1994; 1992-2000.
- 18-Fichsel H, Knöfle G. Effects of anticonvulsant drugs on thyroid hormones in epileptic children. *Epilepsia* 1978; 19: 323-36.
- 19-Deda G, Akıncı A, Teziç T, Karagöl U. Effects of anticonvulsant drugs on thyroid hormones in epileptic children. *Türk J Pediatr* 1992; 34:

239-44.

20-Öğmegül A, Akhan G, Türk S, Gürbilek M. Continuous use of major antiepileptic drugs caused side effects on the hormones, thyroid, testosterone, gonadotrophins and prolactin. *Turk J Resc Med Sci* 1991; 9: 281-5.

21-Yeo PPB, Bates P, Howe JG, Ratcliffe WP. Anticonvulsants and thyroid function. *BMJ* 1978; 1: 1581-3.

22-Yüksel A, Keskin S, Sözüer D, Yalçın E. Uzun süre antikonvülzan ilaç alan epileptik çocuklarda serum tiroid hormonlarının incelenmesi. *Cerrahpaşa Tıp Fak. Der.* 1992; 23: 411-6.

23-Aanderud S, Strandjord RE. Hypothyroidism induced by antiepileptic therapy. *Acta Neurol Scand* 1980; 61: 300-3.

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