Epilepsia, **47**(11):1855–1859, 2006
Blackwell Publishing, Inc.
© 2006 International League Against Epilepsy

The Evaluation of Thyroid Functions, Thyroid Antibodies, and Thyroid Volumes in Children with Epilepsy during Short-Term Administration of Oxcarbazepine and Valproate

*Ali Cansu, *Ayşe Serdaroğlu, †Orhun Çamurdan, *Tuğba Hırfanoğlu, †Aysun Bideci, and *Kıvılcım Gücüyener

*Departments of *Pediatric Neurology; and †Endocrinology, Gazi University Faculty of Medicine, Ankara, Turkey*

Summary: *Purpose*: The aim of this study was to evaluate the effects of short-term oxcarbazepine (OXC) and valproate (VPA) monotherapy on thyroid functions in children.

Methods: Fifty-five newly diagnosed epileptic children with normal thyroid functions (confirmed with the thyrotropin releasing hormone stimulation test) participated in this study. VPA treatment was started in 30 patients and OXC in 25 patients. Serum thyroxine (T_4), free thyroxine (fT_4), triiodothyronine (T_3), free triiodothyronine (fT_3), reverse T3 (rT_3), thyroid peroxidase antibodies (TPO-ab), and urine iodine levels were evaluated at baseline and at the third and sixth months of therapy.

Results: In the OXC group, serum T_4, fT_4, T_3, fT_3, and rT_3 levels were found to be decreased at the third and sixth months, the differences were significant compared to the baseline values except for fT_3 levels at the third month and fT_4 and rT_3 levels at the sixth month ($p < 0.05$). At the sixth month, serum T_4 level dropped below the normal reference value in 8 (32%), fT_4 in 5 (20%), T_3 in 4 (16%), and fT_3 in 3 (12%) patients. In the VPA group, mean T_4, fT_4, T_3, fT_3, and rT_3 levels at 3 and 6 months remained similar compared to the baseline values ($p > 0.05$). Mean serum thyroid stimulating hormone levels increased significantly at the sixth month compared to the baseline values in the VPA group ($p < 0.05$) while it remained unchanged in the OXC group ($p > 0.05$). There was no effect of either drug on urinary iodine excretion and serum TPO-ab levels remained in normal ranges throughout the study.

Conclusions: In this prospective study, it is documented that children under short-term OXC or VPA therapy showed altered thyroid functions similar to the changes observed after long-term treatment. Although, the clinical significance of these results need to be evaluated with future studies, this observation of altered thyroid functions points out that thyroid functions may need to be monitored closely in children receiving antiepileptic treatment, even in the short-time interval. **Key Words:** Epilepsy—Children—Thyroid functions—Oxcarbazepine—Valproate.

There are a large number of studies showing that long-term administration of traditional antiepileptic drugs (AEDs) disturbs thyroid functions (Strandjord et al., 1981; Bentsen et al., 1983; Ericsson et al., 1985; Isojarvi et al., 1989; Brodie and French, 2000). However, there are few studies based on the effect of their short-term effects on thyroid functions (Isojarvi et al., 1995).

Valproate (VPA) is widely used for the treatment of partial and generalized epilepsy in childhood and adolescence (Morton and Pellock, 1996; de Silva et al., 1996; Brodie and French, 2000). Various side effects of VPA on endocrine functions have been reported in the literature (Egger and Brett, 1981; Harden, 2000; Genton et al., 2001; Verrotti et al., 2002). Subclinical hypothyroidism with mild or moderately elevated thyroid stimulating hormone (TSH) levels is one of these, which has been demonstrated in some (Eiris-Punal et al., 1999; Vainionpaa et al., 2004), but not in all studies (Isojarvi et al., 2001; Verrotti et al., 2001).

Oxcarbazepine (OXC) is the 10-keto analog of carbamazepine (CBZ) and is metabolized through different pathways compared to CBZ in the liver (Dam et al., 1989; Isojarvi et al., 2001). CBZ is oxidized while OXC is metabolized mainly by reduction to its active metabolite, 10,11-dihydro-10-hydroxy-carbamazepine (Vainionpaa et al., 2004). Although, OXC is widely used in the treatment of partial epilepsy treatment, there are only a few studies focused on its effects on thyroid functions (Isojarvi et al., 1995; Isojarvi et al., 2001). A study has reported a decrease in serum thyroid hormone levels in children following long-term OXC usage (Vainionpaa et al., 2004).

Accepted June 16, 2006.
Address correspondence and reprint requests to Dr. Ali Cansu, Department of Pediatric Neurology, Gazi University Faculty of Medicine, 06500 Beşevler,/Ankara, Turkey. E-mail: acansu2003@yahoo.com
doi: 10.1111/j.1528-1167.2006.00821.x

To the best of our knowledge, there have been no prospective studies focusing on the effects of short-term OXC and VPA therapy on thyroid functions, thyroid antibody levels, and urinary iodine excretion in children. Therefore, we aimed to investigate these effects in a newly diagnosed epileptic children population.

PATIENTS AND METHODS

Fifty-five newly diagnosed pediatric patients (27 females, 28 males) with partial and generalized epilepsy were enrolled in this study, none of whom were on AEDs or any other drugs that could effect thyroid functions. They had no underlying endocrine, cardiac, neurometabolic, or any other chronic diseases. Their diagnostic tests including cranial magnetic resonance, tandem-mass spectrophotometry, urinary and blood amino acid and organic acid screening were all normal. Additionally, initial thyroid volumes, serum TSH, thyroxine (T_4), free thyroxine (fT_4), triiodothyronine (T_3), free triiodothyronine (fT_3), reverse T3 (rT_3), thyroid peroxidase antibodies (TPO-ab), and urinary iodine levels and the TSH response to the thyrotropin releasing hormone (TRH) stimulation tests were within the normal reference ranges in all patients.

Four patients were excluded because of a high TSH response in the TRH stimulation test, four because of low T4, T3, or fT4 levels, three because of low urinary iodine levels, one because of a multinodular goitre on thyroid USG, and one because of cortical dysplasia on cranial magnetic resonance imaging.

Seizure type description followed the criteria of the International League Against Epilepsy (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). OXC or VPA was started alternatively for patients with partial epilepsy while VPA was used for patients with primary generalized epilepsy. The antiepileptic drug (AED) dose used was chosen according to generally accepted guidelines (Scheuer and Pedley, 1990). OXC and VPA were administered twice daily.

Overall, 25 (15 females and 10 males) patients were started on OXC while the remaining 30 (12 females and 18 males) were put on VPA therapy. The stage of puberty was determined according to Tanner (Tanner and Whitehouse, 1976).

The TRH stimulation test was performed on all patients to determine exact thyroid status. Serum TSH levels were measured at the baseline and at the 20th, 40th, and 60th min after an intravenous injection of TRH (7 μg/kg, maximum 200 μg). Patients with TSH response over 35 μIU/ml TSH units were considered to have subclinical hypothyroidism (Rapaport et al, 1993).

Serum TSH, T_4, T_3, fT_3, fT_4, rT3, TPO-ab, and urinary iodine levels were evaluated at baseline and at the third and sixth months in all patients. Thyroid USG was performed at the beginning of treatment.

Each patient was examined by the same physician at baseline and at the 3rd and 6th months. The clinical status of each patient was noted separately.

Blood samples were obtained between 8.00 and 8.30 a.m. after an overnight fast, and samples were stored frozen at –70°C until analyzed.

ASSAYS

Our laboratory's normal reference ranges are as follows: T_4 5.5–13 μg/dl, fT4 0.8–2.3 ng/ml, T_3 1.19–1.70 ng/ml, fT3 1.8–4.2 pg/ml, rT3 15–35 ng/dl, and basal serum TSH: less than 5 μIU/ml.

Serum TSH, T_4, and T_3 levels were measured with a solid-phase, competitive chemiluminescent enzyme immunoassay, fT_3 and fT_4 concentrations were determined with competitive analog-based immunoassay using the IMMULITE 2000 system.

Serum TPO-ab levels were measured by electrochemiluminescence immunoassay using kits from Roche (Indianapolis, U.S.A.). The measuring range was accepted as 5–600 IU/ml (defined by the lower detection limit and the maximum of the master curve). Antibody levels over 35 U/ml were considered positive, as recommended by the manufacturer. The radioimmunoassay method using the biosource kit was employed for the rT_3 measurement. The minimum detectable concentration of rT_3 has been 0.5 ng/ml and corresponds to the concentration given by two standard deviations below the mean cpm of 10 replicate determinations of the zero standard. Urine iodine concentration was determined by the Wawcshinek method, Sandel-Kolthoff (Dunn et al., 1993; Delange, 1994).

Serum VPA concentration was analyzed with a fluorescence polarization immunoassay system using the AxSym analyzer (Abbott Diagnostic Division, Irving, Texas, U.S.A.). The serum concentrations of monohydroxycarbamazepine (the active metabolite of OXC) were determined by high-performance liquid chromatography.

Thyroid volumes were measured with USG by the same physician using the formula of the ellipsoid model proposed by Brunn et al. (volume [ml] = 0.479 × three dimensions [cm]), by adding right and left lobes, excluding the volume of the isthmus (Brunn et al., 1981).

The paired samples *t*-test was used in order to compare data at baseline and the third and the sixth months. Correlation between the parameters was assessed with the Pearson correlation coefficients.

A consent form was obtained from all the patients and/or their parents. Approval for the study was obtained from the Gazi University Faculty of Medicine Ethics Committee.

RESULTS

The clinical characteristics of the children participating in the study are given in Table 1.

Thyroid functions in children treated with OXC are given in Table 2. Although did not reach clinical

TABLE 1. *Clinical characteristics of the patients receiving antiepileptic monotherapy*

	n	Age (years)	Dosage (mg/kg/day) 20	25	30	35	40	Type of epilepsy P	G	Puberty stage Prepuberal	Pubertal	DSC (μg/ml) Month 3	Month 6
OXC	25	6.46 ± 2.2			14	7	4	25	0	17	8	15.14 ± 3.01	16.22 ± 4.13
VPA	30	10.05 ± 4.59	2	6	14	8		16	14	14	16	75.04 ± 13.66	71.17 ± 24.6

OXC, oxcarbazepine; VPA, valproate; P, partial; G, generalized; DSC, drug serum concentration.

significance for every hormone analyzed at each follow-up interval, in general, thyroid hormone values tended to decrease at the third and the sixth months compared to baseline values in patients treated with OXC. Eight patients (32%) had serum T_4, five patients (20%) had serum fT_4, four (16%) had serum T_3, and three (12%) had serum fT_3 levels below the reference range at the sixth month. Serum TSH levels remained within the normal range throughout the study period.

Mean thyroid hormone levels remained similar throughout the study period in patients treated with VPA (Table 3). On the other hand, one patient (3%) had serum T_4, T_3, and fT_3 and two patients (6.6%) had serum fT_4 levels below the reference range at sixh month. Serum TSH levels tended to increase throughout the study with the difference reaching a significant level at the sixth month.

TPO-Ab remained in normal levels throughout the study. Neither drug had an effect on urinary iodine excretion ($p > 0.05$) (Tables 2 and 3).

There were no correlations between serum drug concentrations and thyroid hormone levels in either groups (data not shown). There was no impact of pubertal stage on changes of thyroid status in either groups (data not shown).

TABLE 2. *Laboratory data in children treated with OXC**

OXC	Pretreatment (Month 0)	Month 3	Month 6
T4 (μg/dl)	8.38 ± 1.85	7.06 ± 2.14[b]	6.94 ± 2.04[c]
fT4 (ng/ml)	1.38 ± 0.23	1.24 ± 0.28[c]	1.26 ± 0.31
T3 (ng/ml)	1.32 ± 0.19	1.26 ± 0.19[a]	1.24 ± 0.22[b]
fT3 (pg/ml)	3.07 ± 0.46	2.91 ± 0.59	2.85 ± 0.54[a]
TSH (μIU/ml)	2.48 ± 1.17	2.47 ± 0.97	2.57 ± 0.99
rT3 (ng/dl)	30.75 ± 14.58	23.49 ± 13.16[a]	24.41 ± 15.12
Patients with elevated TPO-ab	None	None	None
Urinary iodine (μg/dl)	12.94 ± 2.76	16.31 ± 2.96	13.29 ± 2.71
Thyroid volumes (ml)	3.76 ± 1.68		

Group versus baseline; [a]$p < 0.05$. [b]$p < 0.01$. [c]$p < 0.001$.

*Values are expressed as Mean ± SD; the paired samples *t*-test was used for T4, fT4, T3, fT3, TSH, rT3, TPO-ab, and urinary iodine.

OXC, Oxcarbazepine; T4, thyroxine; fT4, free thyroxine; T3, triiodothyronine; fT3, free triiodothyronine; TSH, thyrotropin; rT3, reverse triiodothyronine; TPO-ab, antibodies to thyroid peroxidase.

DISCUSSION

This is the first prospective study focused on the effects of short-term OXC and VPA treatment on thyroid functions in children. Recently, in cross-sectional studies considering long-term OXC treatment, serum T_4, and/or fT_4 levels decreased below the normal reference values in 24% of adult patients and in more than half of children (Isojarvi et al., 2001; Vainionpaa et al., 2004). Our study reveals that these changes occur even in the early stages of OXC therapy in children. This is of particular importance, because short-term OXC treatment in adults is reported to have no deleterious effect on thyroid hormone status (Isojarvi et al., 1995). Whether this effect is solely the consequence of liver enzyme induction is still a matter of discussion. Studies reveal that there is no correlation between liver enzyme levels and thyroid hormone status and no correlation could be established between drug dosage and thyroid hormone levels in patients using OXC, neither in our study nor in others (Isojarvi et al., 2001; Vainionpaa et al., 2004). Besides, although the degree of enzyme induction observed in OXC use is lower than that of CBZ (Larkin et al., 1991), the effects of these two drugs on thyroid hormone levels are similar (Isojarvi et al., 2001), leading to the suggestion that there shall be some other mechanisms by which OXC effect thyroid hormone status (Isojarvi et al., 2001; Vainionpaa et al., 2004).

TABLE 3. *Laboratory data in children treated with VPA*

OXC	Pretreatment (Month 0)	Month 3	Month 6
T4 (μg/dl)	8.72 ± 2.03	8.25 ± 1.76	8.32 ± 1.81
fT4 (ng/ml)	1.37 ± 0.21	1.29 ± 0.2	1.29 ± 0.25
T3 (ng/ml)	1.4 ± 0.29	1.3 ± 0.25	1.31 ± 0.38
fT3 (pg/ml)	3.29 ± 0.69	3.21 ± 0.78	3.16 ± 0.74
TSH (μIU/ml)	2.46 ± 1.07	2.98 ± 1.38	3.17 ± 1.53[a]
rT3 (ng/dl)	26.94 ± 11.62	26.97 ± 12.95	27.38 ± 13.47
Patients with elevated TPO-ab	None	None	None
Urinary iodine (μg/dl)	13.11 ± 2.91	11.98 ± 2.68	12.39 ± 2.41
Thyroid volumes (ml)	5.4 ± 2.14		

Mean ± SD; the paired samples *t*-test was used for T4, fT4, T3, fT3, TSH, rT3, TPO-ab, and urinary iodine.

Group versus baseline; [a]$p < 0.01$.

VPA, valproate; T4, thyroxine; fT4, free thyroxine; T3, triiodothyronine; fT3, free triiodothyronine; TSH, thyrotropin; rT3, reverse triiodothyronine; TPO-ab, antibodies to thyroid peroxidase.

Competition of AEDs with thyroid hormones to bind to thyroxine-binding globulin (TBG), as Surks and DeFesi (1996) suggested could be one of these, but if so, one would expect free thyroid hormone levels to be increased as the drugs separate T4 from TBG (Surks and Sievert, 1995). The fact that free hormone levels were also found to be decreased in our study indicates that this theory could not be valid for OXC.

Serum TSH levels remained stable in patients using OXC despite the decrease in thyroid hormones in our study, as also shown in previous studies (Isojarvi et al., 2001; Vainionpaa et al., 2004). The current literature offers two possible explanations for the lack of the expected increase in serum TSH levels; either a new balance in tissue level is formed so that even the decreased hormone levels are satisfactory enough to perform the metabolic activities needed by the tissue (McDermott and Ridgway, 2001; Verrotti et al., 2001), or it is due to a lack of TSH response because of the disturbed hypothalamus-hypophysis-thyroid axis (Vainionpaa et al., 2004). If the latter is true, even though patients are considered to be clinically euthyroid, it may pose a long-term risk in childhood. Besides, rT3 level, which is considered to be an indirect indicator of thyroid hormones at the tissue level is also decreased significantly at third month in our OXC group. Considering the children to be "euthyroid" by means of measurable clinical parameters (i.e., blood pressure, pulse rate, etc.) may not clearly reflect long-term side effects of this decreased thyroid hormone levels. In general, it is shown that in childhood, minor changes in thyroid metabolism—even in the case of "subclinical hypothyroidism" which is defined with normal thyroid hormone levels and clinically euthyroid status lead to problems such as somatic symptoms, depression, poor memory, slow thinking, cognitive impairment, and subtle neuromuscular abnormalities in the long-term (Isojarvi et al., 1990; Monzani et al., 1993; Monzani et al., 1999; Jensovsky et al., 2002; Schindler, 2003). Our study, considering only short time interval and thyroid hormone levels, does not provide data about this hypothesis. To the best of our knowledge, the literature also lacks the particular interest of the "subclinical" side effects of the changes in thyroid functions in children on AEDs. Therefore, the postulation that the same problems may gradually develop in clinically euthyroid children using OXC needs to be confirmed or ruled out by prospective, controlled long-term studies.

Although there are studies considering the effects of VPA on thyroid functions, they are not clearly documented prospectively in children under short-term treatment (Isojarvi et al., 2001; Verrotti et al., 2002; Vainionpaa et al., 2004). The only parameter that changed significantly in our VPA group of patients were the increased serum TSH levels. There are other studies in which thyroid hormone levels are found to be unchanged while TSH levels increase in patients using VPA (Isojarvi et al., 1989; Isojarvi et al., 2001; Vainionpaa et al., 2004). The clinical significance of this increase is uncertain but seems to be a compensatory response in at least some of the patients. Eiris-Punal et al. (1999) found subclinical hypotyhyroidism in 26% of their patients using VPA therapy. We were not able to perform TRH stimulation test at the sixth month, so it remains unclear whether our children using VPA developed "subclinical hypothyroidism."

Consistent with previous reports (Isojarvi et al., 2001; Vainionpaa et al., 2004), antiTPO-ab levels remained unchanged in either groups in our study. This indicates that autoimmune mechanisms are not responsible for the altered thyroid functions observed in our patients.

The effect of AEDs on thyroid volumes is also a matter of interest. Increase in the size of the thyroid glands has been reported in patients taking either CBZ or phenytoin for epilepsy, and it was suggested to be compensatory due to low serum thyroid hormone concentration (Hegedüs et al., 1985). We did not perform thyroid USGs in the follow-up of our patients because we thought that our follow-up period would not be long enough for this effect to take place.

The limitation of our study is that we were not able to form a control group because of ethical reasons. This limitation may be omitted with the prospective design, using baseline values as the controls.

In conclusion, our study, being the first prospective one considering thyroid status in short-term treatment of VPA and OXC in children has revealed that both OXC and VPA influence thyroid functions. Although the clinical significance of these effects are not documented in our study, considering the data in literature revealing minor changes in thyroid status in childhood lead to negative effects that cannot be determined with routine clinical examinations, we believe that our study suggests that thyroid status should be monitored closely in children using VPA or OXC even in the short-term interval. For this suggestion to be emphasized, prospective studies that consider fine cognitive and developmental changes are needed.

REFERENCES

Bentsen KD, Gram L, Veje A. (1983) Serum thyroid hormones and blood folic acid during monotherapy with carbamazepine or valproate. A controlled study. *Acta Neurol Scand* 67:235–241.

Brodie MJ, French JA. (2000) Management of epilepsy in adolescents and adults. *Lancet* 356:323–329.

Brunn J, Block U, Ruf G, Bos I, Kunze WP, Scriba PC. (1981) Volumetrie der schildrusenlappen mittels real-time-sonografie. *Dtsch Med Wochenschr* 106:1338–1341.

Commission on Classification and Terminology of the International League Against Epilepsy. (1989) Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 30:389–399.

Dam M, Ekberg R, Leyning Y, Waltimo O, Jakobsen K. (1989) A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed. Previously untreated epilepsy. *Epilepsy Res* 3:70–76.

de Silva M, MacArdle B, McGowan M, Hughes E, Stewart J, Neville BG, Johnson AL, Reynolds EH. (1996) Randomised comparative

monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. *Lancet* 347:709–713.

Dunn JT, Crutchfield HE, Gutekunst R, Dunn AD. (1993) Two simple methods for measuring iodine in urine. *Thyroid* 3:119–123.

Egger J, Brett EM. (1981) Effects of sodium valproate in 100 children with special reference to weight. *Br Med J* 283:577–581.

Eiris-Punal J, Del Rio-Garma M, Del Rio-Garma MC, Lojo-Rocamonde S, Novo-Rodriguez I, Castro-Gago M. (1999) Long-term treatment of children with epilepsy with valproate or carbamazepine may cause subclinical hypothyroidism. *Epilepsia* 40:1761–1766.

Ericsson UB, Bjerre I, Forsgren M, Ivarsson SA. (1985) Thyroglobulin and thyroid hormones in patients on long-term treatment with phenytoin, carbamazepine, and valproic acid. *Epilepsia* 26:594–596.

Delange F. (1994) Iodine. *Ann Nestle* 52:81–93.

Genton P, Bauer J, Duncan S, Taylor AE, Balen AH, Eberle A, Pedersen B, Salas-Puig X, Sauer MV. (2001) On the association between valproate and polycystic ovary syndrome. *Epilepsia* 43:295–304.

Harden CL. (2000) Therapeutic safety monitoring: what to look for and when to look for it. *Epilepsia* 41:S37–S44.

Hegedüs L, Hansen JM, Luhdorf K, Perrild H, Feldt-Rasmussen U, Kampmann JP. (1985) Increased frequency of goitre in epileptic patients on long-term phenytoin or carbamazepine treatment. *Clin Endocrinol* 23:423–429.

Isojarvi JIT, Airaksinen KE, Mustonen JN, Pakarinen AJ, Rautio A, Pelkonen O, Myllyla VV. (1995) Thyroid and myocardial function after replacement of carbamazepine by oxcarbazepine. *Epilepsia* 36:810–816.

Isojarvi JI, Pakarinen AJ, Myllyla VV. (1989) Thyroid function in epileptic patients treated with carbamazepine. *Arch Neurol* 46:1175–1178.

Isojarvi JIT, Pakarinen AJ, Ylipalosaari PJ, Myllyla VV. (1990) Serum hormones in male epileptic patients receiving anticonvulsant medication. *Arch Neurol* 47:670–676.

Isojarvi JIT, Turkka J, Pakarinen AJ, Kotila M, Rattya J, Myllyla VV. (2001) Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. *Epilepsia* 42:930–934.

Jensovsky J, Ruzicka E, Spackova N, Hejdukova B. (2002) Changes of event related potential and cognitive processes in patients with subclinical hypothyroidism after thyroxine treatment. *Endocr Regul* 36:115–122.

Larkin JG, McKee PJW, Forrest G, Beastall GH, Park BK, Lowrie JI, Lloyd P, Brodie MJ. (1991) Lack of enzyme induction with oxcarbazepine (600 mg daily) in healthy subjects. *Br J Clin Pharmacol* 31:65–71.

McDermott MT, Ridgway EC. (2001) Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Metab* 86:4585–4590.

Monzani F, Caraccio N, Del Guerra P, Casolaro A, Lippolis PV, Goletti O. (1999) Neuromuscular symptoms and dysfunction in subclinical hypothyroid patients: beneficial effect of L-T4 replacement therapy. *Clin Endocrinol* 51:237–242.

Monzani F, Del Guerra P, Caraccio N, Pruneti CA, Pucci E, Luisi M, Baschieri L. (1993) Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment. *Clin Investig* 71:367–371.

Morton LD, Pellock JM. (1996) Diagnosis and treatment of epilepsy in children and adolescents. *Drugs* 51:399–414.

Rapaport R, Sılls I, Patel U, Oppenheimer E, Skuza K, Horlick M, Goldstein S, Dimartino J, Saenger P. (1993) Thyrotropin-releasing hormone stimulation tests in infants. *J Clin Endocrinol Metab* 77:889–894.

Scheuer ML, Pedley TA. (1990) The evaluation and treatment of seizures: current concepts. *N Engl J Med* 323:1468–1474.

Schindler AE. (2003) Thyroid function and postmenopause. *Gynecol Endocrinol* 17:79–85.

Strandjord RE, Aanderud S, Myking OL, Johannessen SI. (1981) Influence of carbamazepine on serum thyroxine and triiodothyronine in patients with epilepsy. *Acta Neurol Scand* 63:111–121.

Surks MI, DeFesi CR. (1996) Normal serum free thyroid hormone concentrations in patients treated with phenytoin or carbamazepine. *JAMA* 275:1495–1498.

Surks MI, Sievert R. (1995) Drugs and thyroid function. *N Engl J Med* 333:1688–1693.

Tanner JM, Whitehouse RH. (1976) Clinical longitudinal standards for height, weight, height velocity and stages of puberty. *Arch Dis Child* 51:170–182.

Vainionpaa LK, Mikkonen K, Rattya J, Knip M, Pakarinen AJ, Myllyla VV, Isojarvi JI. (2004) Thyroid function in girls with epilepsy with carbamazepine, oxcarbazepine, or valproate monotherapy and after withdrawal of medication. *Epilepsia* 45:197–203.

Verrotti A, Basciani F, De Simone M, Trotta D, Morgese G, Chiarelli F. (2002) Insulin resistance in epileptic girls who gain weight after therapy with valproic acid. *J Child Neurol* 17:265–268.

Verrotti A, Basciani F, Morresi S, Morgese G, Chiarelli F. (2001) Thyroid hormones in epileptic children receiving carbamazepine and valproic acid. *Pediatr Neurol* 25:43–46.