Thyroid hormones in children with epilepsy during long-term administration of carbamazepine and valproate

Alberto Verrotti, Melissa Laus, Alessandra Scardapane, Emilio Franzoni and Francesco Chiarelli
Department of Pediatrics, University of Chieti, Via dei Vestini 5, 66100 Chieti, Italy and Department of Child Neuropsychiatry, University of Bologna, Bologna, Italy
(Correspondence should be addressed to A Verrotti; Email: averrott@unich.it)

Abstract
Objective: This study evaluates the effects of long-term carbamazepine (CBZ) and valproate acid (VPA) therapy on thyroid function in epileptic children.
Design: A prospective study performed in 32 newly diagnosed pediatric patients, subdivided into two groups: 18 patients treated with CBZ and 14 patients treated with VPA. Thirty-two sex- and age-matched subjects served as controls.
Methods: Serum TSH, thyroxine (T4), triiodothyronine (T3), free thyroxine (fT4), free triiodothyronine (fT3), thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies (TG-Ab) were evaluated at baseline and at the 3rd, 6th, and 12th month in all patients and in the control group. A TRH stimulation test was performed in all epileptic patients at baseline and at the 3rd, 6th, and 12th month evaluations while in controls only baseline assessment was carried out.
Results: At baseline evaluation, thyroid function was normal in all epileptic children. After 3 months, CBZ-treated patients showed serum T4 and fT4 levels significantly lower than baseline evaluation and control subjects. Serum T4 and fT4 concentrations were unaffected by VPA monotherapy. Serum T3 and fT3 were normal in both CBZ-treated and VPA-treated patients. TRH test was normal in all patients. At 6th and 12th month evaluations, the same alterations were present in CBZ-treated patients while thyroid function remained normal in VPA-treated patients. TRH test responses were normal in all epileptic patients. TPO-Ab and TG-Ab were always absent in all patients.
Conclusions: Our data suggest that VPA monotherapy does not alter thyroid hormones. On the contrary, alterations of thyroid hormones occur in CBZ-treated children. However, the patients are euthyroid and thyroid hormone alterations are not associated with clinical or subclinical hypothyroidism.

Introduction
Carbamazepine (CBZ) is considered one of the first drugs in treatment of partial and secondarily generalized seizures (1, 2). Valproic acid (VPA) has also been found to be an effective antiepileptic drug (AED) in epilepsy (3, 4). Although these AEDs are well tolerated, many effects on endocrine function have been reported in literature (5–8). The effect of these two AEDs on serum thyroid hormone concentrations has been controversial: CBZ therapy can decrease the serum thyroid hormone levels, but generally serum thyrotropin-releasing hormone (TSH) concentrations remain normal except in a small percentage of patients who show increased TSH levels (9, 12). Different thyroid dysfunctions have been reported in epileptic patients receiving VPA. In particular, reports on the effect of VPA on the thyroid hormones balance are conflicting, and both low and unchanged serum thyroxine (T4) and free thyroxine (fT4) levels have been found in patients receiving VPA monotherapy, never associated with overt thyroid dysfunction (9–14): these studies showed normal mean TSH serum levels while other studies documented high TSH levels in patients receiving VPA therapy (10–12). However, the majority of studies have been performed in adult patients receiving these drugs, often in association with other AEDs.

In the present study, changes in serum thyroid hormone levels during CBZ and VPA therapy were analyzed prospectively, and thyroid hormone concentrations have been evaluated after the TSH test in a group of epileptic children taking these drugs.

Subjects and methods
Thirty-two pediatric patients with partial and generalized epilepsy were enrolled in this study. In particular, 20 patients suffered from primary generalized seizures, including two patients with absence seizures, and 12 patients suffered from partial seizures (two patients with secondary generalization). Seizure type description followed the criteria of the International League Against
Epilepsy (15). Their mean ± s.d. age was 7.2 ± 3.1 years. Mean height ± s.d. was 125.6 ± 2.7 cm; mean weight ± s.d. was 25.9 ± 3.4 kg (Table 1). Bone age of all patients was correspondent to chronological age.

At the beginning of the study, all patients were prepubertal (Tanner stage I; P1 B1 for female subjects and P1 G1 for male subjects), and they remained exactly as this for the entire duration of the study. The main criteria for exclusion from the study were: abnormal neurological examination, abnormal cerebral computed tomography and/or magnetic resonance imaging scan; thyroid, liver, or kidney diseases; endocrinopathies; and chromosomal abnormalities. Moreover, we studied 32 sex- and age-matched controls. Controls came from children of the same geographical area and were admitted to the department of pediatrics for other reasons than endocrine problems (e.g. upper respiratory airway mild infections, enteritis, minor head trauma, etc). In all children, thyroid function was measured after the complete resolution of their disease in order to exclude the interference of their pathologies on thyroid function.

The informed consent of the study has been signed by the parents and peers of all patients enrolled; consent for the study was obtained also in the control group. The study (including TRH-tests in controls) was approved by the Ethics Committee of the Faculty of Medicine, University of Chieti.

We performed evaluations before the beginning of antiepileptic therapy and at 3, 6, and 12 months after the start of treatment. Our baseline evaluation was performed to document possible previous thyroid dysfunctions and to detect if epilepsy itself can cause thyroid dysfunction.

All patients began antiepileptic therapy after at least two febrile seizures. CBZ and VPA were prescribed at the normal dosages: CBZ 25.9 ± 7.1 mg/kg per day and VPA 27.2 ± 7.4 mg/kg per day. Serum levels of CBZ and VPA were within therapeutic ranges (Table 1). No patients had serum levels of CBZ and VPA above the therapeutic range. CBZ and VPA were administered in two doses. No other drugs were prescribed. The pertinent data of the groups of patients and controls are listed in Table 1. Serum T4, triiodothyronine (T3), fT4, free triiodothyronine (T3), fT4, and TSH, were performed by RIA (Biodata Kits, Milano, Italy). The sensitivity of the T3 assay was 5 nmol/l, the coefficient of intra-assay variation was 4.5%, and the coefficient of inter-assay variation was 5.7%. The respective values for T3 assay were 0.1 nmol/l, and 5.1%, and 6.2%. The sensitivity of TSH assay was 0.03% mlU/l. The intra-assay variation and the inter-assay variation were 5.4 and 6% respectively. The sensitivity of the fT3 assay was 0.13 pmol/l, the intra-assay variability was 4.4%, and the inter-assay variability 5%; the sensitivity of the fT3 assay was 0.12 pmol/l, the intra-assay variability was 3.4%, and the inter-assay variability 4.1%.

Serum TSH, T4, T3, fT4, fT3, thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies (TG-Ab) were evaluated at baseline and at the 3rd, 6th, and 12th months in all patients and also in the control group. Blood samples were obtained between 0800 and 0830 h.

**Table 1** Serum thyroid hormone concentrations and TRH-stimulated concentrations in epileptic patients and in control subjects.

<table>
<thead>
<tr>
<th></th>
<th>CBZ-treated patients</th>
<th>VPA-treated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control before therapy</td>
<td>After 3 months of therapy</td>
</tr>
<tr>
<td>Number of patients</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>15/17</td>
<td>9/10</td>
</tr>
<tr>
<td>Age (year)</td>
<td>7.5 ± 2.5</td>
<td>6.5 ± 3.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>125.2 ± 1.8</td>
<td>125.4 ± 2.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>25.5 ± 2.5</td>
<td>25.6 ± 3.1</td>
</tr>
<tr>
<td>Dosage (mg/kg per day)</td>
<td>25.9 ± 7.1</td>
<td>27.9 ± 6.9</td>
</tr>
<tr>
<td>AEDs levels (μg/ml)</td>
<td>7.2 ± 1.8</td>
<td>7.0 ± 2.1</td>
</tr>
<tr>
<td>T4 (nmol/l)</td>
<td>91.9 ± 15.1</td>
<td>89.7 ± 17.9</td>
</tr>
<tr>
<td>fT4 (pmol/l)</td>
<td>16.1 ± 3.0</td>
<td>17.4 ± 2.9</td>
</tr>
<tr>
<td>T3 (nmol/l)</td>
<td>1.6 ± 0.5</td>
<td>1.6 ± 0.8</td>
</tr>
<tr>
<td>fT3 (pmol/l)</td>
<td>2.9 ± 0.9</td>
<td>2.7 ± 0.9</td>
</tr>
<tr>
<td>TSH basal (mIU/l)</td>
<td>2.4 ± 0.9</td>
<td>2.5 ± 0.9</td>
</tr>
<tr>
<td>TSH peak (mIU/l)</td>
<td>15.5 ± 3.6</td>
<td>15.9 ± 4.0</td>
</tr>
<tr>
<td>Peak time (min)</td>
<td>20.2 ± 1.7</td>
<td>20.1 ± 1.8</td>
</tr>
<tr>
<td>TSH 1 h after TRH (mIU/l)</td>
<td>9.1 ± 3.9</td>
<td>9.9 ± 4.1</td>
</tr>
</tbody>
</table>

*P<0.001 versus controls and baseline evaluation.

www.eje-online.org
after overnight fast, and samples were stored frozen at –70 °C until analyzed within 12 months after sample collection. TRH stimulation test was performed in all patients to determine exact thyroid status. Serum TSH levels were measured at the baseline and at the 20th, 40th, and 60th minutes after an i.v. 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 (16). Serum TPO-Ab and TG-Ab levels were measured with RIA using kits from Brahms Diagnostica (Berlin, Germany). In both tests, as recommended by the manufacturer, antibody levels 60 U/ml were considered to be increased. Serum CBZ and VPA concentration were assayed with fluorescence polarization immunoassay, using a TDX analyzer (Abbot Division).

Statistical analysis
Data are expressed as mean ± S.D. values and analyzed using the statistical package for social sciences (SPSS 8.0, Chicago, IL, USA). When one group of patients was compared with controls, the Student t-test was applied. The data of the patients at different times of the study (at baseline and the 3rd, 6th, and 12th months) were evaluated by ANOVA for repeated measures. The relationship between thyroid hormone concentrations and CBZ and VPA daily dosages and their serum concentrations were examined by linear regression and Spearman’s correlation coefficient analyses. P value less than 0.05 were considered significant.

Results
Baseline evaluation
Thyroid function was normal in all epileptic children: no difference was found between patients and controls. Moreover, TSH responses to TRH test were similar in epileptic patients and in controls (Table 1). After TRH injection the mean peak values occurred at 20 min after TRH injection in all subjects except in one patient treated with VPA who showed the peak value at 15 min.

Follow-up evaluations at 3rd month
CBZ treated patients showed serum T₄ and fT₄ levels significantly lower than baseline evaluation and control subjects. Serum T₄ and fT₄ concentrations were unaffected by VPA monotherapy. Serum T₃ and fT₃ were normal in both CBZ-treated and VPA-treated patients. TRH test was normal in all patients: we found no significant difference in mean peak values and in the times of peak concentration between patients and controls and between the two groups of VPA and CBZ-treated children. No significant differences in the auxological parameters considered were found between the two groups of patients and control subjects.

Follow-up evaluation at 6th and 12th months
The above-mentioned changes were still present in CBZ treated patients, while VPA treated patients continued to have normal thyroid function. TRH test response persisted normal in all epileptic patients. TPO-Ab and TG-Ab remained in normal levels throughout the study.
No significant correlations were found between the levels of all thyroid hormones and the mean daily AEDs dosages and serum AEDs concentrations, in the two groups of patients. At the follow-up evaluations, the two groups of patients and control subjects remained similar for height and weight.

Therapy withdrawal evaluation
In 5 out of 18 CBZ-treated children, CBZ therapy has been withdrawn. Six months after withdrawal, reevaluation of hormone levels found that all values were normal, without any significant differences with respect to control and baseline levels (see Figs 1 and 2).
Six months after withdrawal, no significant differences were present in all growth parameters.

Discussion
This is the first prospective study focused on the effects of long-term CBZ and VPA treatment on thyroid function in children.
We performed a baseline evaluation and a long-term follow-up. Previous studies (17, 18) have reported some endocrine abnormalities linked to epilepsy, but our baseline evaluation allowed us to exclude the possibility that thyroid abnormalities can be the result of the convulsive disorder itself (or from other situations like congenital thyroid diseases).
Our follow-up study demonstrates that in CBZ-treated children, serum T₄ and fT₄ concentrations are lower than in controls, whereas T₃, fT₃, and TSH are normal.
A Verrotti and others

with low serum fT4 concentrations did not have that serum T4 and fT4 decreased whereas TSH levels remained unchanged. The patients with low serum thyroid hormone levels appeared clinically euthyroid; therefore, the clinical significance of this decrease seems to be minimal; it is possible that CBZ influences the active transmembrane transport of T4 (and not T3) in the various tissues (including hypothalamus/pituitary). This hypothesis can explain the euthyroid status of our patients.

Our follow-up demonstrates that the change in fT4 is already present after 3 months of therapy and persists in the next months: this effect of CBZ treatment is clearly present just after the first month of therapy and persists through the entire treatment. CBZ-related changes of serum fT4 concentrations have been attributed to induction of the hepatic **P-450 enzyme system: inducing this hepatic system, CBZ is able to increase thyroid hormone metabolism (25, 27). The patients with low serum thyroid hormone levels did not have increased levels of serum TPO-Ab or TG-Ab. Therefore, the altered thyroid function in patients taking CBZ did not seem to be mediated by the activation of autoimmune mechanisms. The clinical significance of changes in serum thyroid hormone concentrations during CBZ treatment remained unknown.

On the contrary, our children receiving VPA did not manifest any significant abnormalities of thyroid hormones. These data are in agreement with previous papers that found normal thyroid hormone levels (19, 20, 25, 28–30). By contrast, other studies (11, 31) found normal thyroid hormone levels while TSH levels were increased. In a recent study, 36 out of 143 patients had TSH > 5 m IU/l (index of subclinical hypothyroidism) during VPA treatment: 10 out of these patients also had low fT4 levels; 9 out of these 36 patients had clinical symptoms of hypothyroidism but they are considered to have subclinical hypothyroidism because of high TSH values (32). The clinical significance of this increase is uncertain but seems to be a compensatory response in at least some of the patients. No association was also found between serum thyroid hormone concentrations and VPA related obesity (30, 33).

To evaluate the hypothalamic–hypophysis–thyroid axis, TRH test was performed in the two groups of patients, and depicted normal values in all children studied. The TSH stimulation test was originally introduced to assist in the diagnosis of hypothalamus–hypophysis–thyroid axis alterations and evaluations of pituitary TRH reserve; the TRH assays of that time had poor sensitivity and were unable to distinguish between normal and low unstimulated TSH concentration (34–36). Furthermore, it was claimed that the TRH test could differentiate pituitary and hypothalamic lesions, with an exaggerated or delayed TSH response that can be suggestive of hypothalamic dysfunction or a compressed pituitary stalk (37–42). The TRH test performed in this study showed peak response to TRH injection at 20 min in all patients (except one VPA-treated patient who showed the peak value at 15 min) suggesting the integrity of the hypothalamus and pituitary. Some authors suggested a possible inhibitory effect of some AEDs on the hypothalamic and/or anterior pituitary hormone levels (43, 44). Because the TRH-stimulated TSH responses were unaltered by these drugs, we are against this hypothesis. Blank and Joffe (33, 45) suggested that CBZ may alter thyroid hormone levels affecting directly TSH or TRH, but our data do not support this possibility. In agreement with other authors (5, 19, 26), TSH levels do not increase in CBZ-treated patients, the cause is not activated by the positive feedback mechanism, which should result from low serum thyroid hormone concentrations and serum thyroid hormone levels remain low. Moreover, TRH-stimulated secretion of TSH is not increased during CBZ medication. Therefore, it is possible that an impairment of thyroid function can occur during CBZ medication and a long-term follow-up is necessary in the case of long-term use of this drug.

In 5 out of 18 patients, withdrawal of CBZ therapy, restoration of normal thyroid hormone levels resulted after 6 months from the end of therapy. These results suggest that the changes in serum fT4 levels are reversible. Our experience of 5 patients who have withdrawn CBZ-therapy is in agreement with previous reports (27, 11).

In conclusion, our data suggest that the VPA monotherapy does not alter serum levels of thyroid hormones. On the contrary, alterations of thyroid function clearly occur in children treated with CBZ. However, the patients are euthyroid and low serum fT4 concentrations during CBZ medication are not associated with clinical or even subclinical hypothyroidism. All these CBZ induced changes are reversible.
Declaration of interest
We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

Carbamazepine and valproate and thyroid function

www.eje-online.org


Received 21 October 2008
Accepted 24 October 2008