Original article

Epileptic Disord 2016; 18 (2): 181-86

Duration of valproic acid monotherapy correlates with subclinical thyroid dysfunction in children with epilepsy

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Received December 02, 2015; Accepted February 16, 2016

ABSTRACT – *Aim.* To identify potential risk factors for the development of subclinical hypothyroidism following long-term valproic acid monotherapy in children with epilepsy.
Methods. Serum levels of thyroid-stimulating hormone, free thyroxine, free triiodothyronine, thyreoglobulin antibodies, and thyroid peroxidase antibodies were determined in 41 patients and in 41 sex- and age-matched healthy children.
Results. Mean valproic acid treatment duration was 2.80±1.96 years. The valproic acid group had higher serum thyroid-stimulating hormone ($p<0.001$) and free triiodothyronine ($p<0.05$) levels compared to the control group. Serum thyroid-stimulating hormone and free triiodothyronine were above the upper limit for healthy controls in 34% and 32% of patients, respectively, and no clinical features of thyroid dysfunction were observed. Duration of valproic acid monotherapy for less than four years was a risk factor for elevated thyroid-stimulating hormone levels.
Conclusion. One third of children with normal range serum valproic acid levels may have elevated serum thyroid-stimulating hormone and free triiodothyronine levels, especially in the first four years of treatment.

Key words: children, epilepsy, valproic acid, thyroid function

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doi:10.1684/epd.2016.0821

Epilepsy is the most common neurological disorder in childhood. The primary treatment option is the use of antiepileptic drugs (AEDs) and patients often require long-term and sometimes life-long treatment (Freitag *et al.*, 2001). However, the use of AEDs has been associated with thyroid disorders, in particular subclinical hypothyroidism, in paediatric patients (Caksen *et al.*, 2002; Castro-Gago *et al.*, 2007; Hirfanoglu *et al.*, 2007). This is a major concern for clinicians since it has been demonstrated that even minor changes in thyroid metabolism during childhood may cause growth and developmental disorders, as

well as cognitive impairment and subtle neuromuscular abnormalities (Monzani *et al.,* 1993; Jensovsky *et al.,* 2002; Setian, 2007).

Decreased levels of free thyroxine (FT4) and free triiodothyronine (FT3) with unchanged or elevated levels of thyroid stimulating hormone (TSH) were shown in several studies with carbamazepine, oxcarbazepine and phenobarbital (Cansu *et al.,* 2006; Hirfanoglu *et al.,* 2007; Verrotti *et al.,* 2009; Aggarwal *et al.,* 2011; Turan *et al.,* 2014; Kafadar *et al.,* 2015), but the association between the use of valproic acid (VPA) and thyroid dysfunction remains controversial. Some studies showed that VPA leads to subclinical hypothyroidism with TSH levels in the range of 5-25 mIU/l or significantly higher than those of the control group, and unchanged or decreased levels of FT3 and FT4 (Vainionpaa *et al.,* 2004; Cansu *et al.,* 2006; Castro-Gago *et al.,* 2007; Hirfanoglu *et al.,* 2007; Mikati *et al.,* 2007; Attilakos *et al.,* 2009; Aggarwal *et al.,* 2011; Aygun *et al.,* 2012), while others reported no significant change in the homeostasis of thyroid hormones (Specchio *et al.,* 1985; Tanaka *et al.,* 1987; Verrotti *et al.,* 2001; Caksen *et al.,* 2002; Verrotti *et al.,* 2009).

Moreover, there seems to be even more controversy regarding risk factors for thyroid dysfunction, such as age, duration of VPA treatment, daily dosage, and serum level of the drug. Some studies showed an association of age and/or duration of VPA treatment with thyroid hormone imbalance (Mikati *et al.,* 2007; Sahu *et al.,* 2012), while others have reported opposing results (Tanaka *et al.,* 1987; Castro-Gago *et al.,* 2007; Hirfanoglu *et al.,* 2007). In addition, significant correlations between the levels of thyroid hormones and VPA daily dosage or serum concentration have been reported (Kim *et al.,* 2012).

The aim of this study was to investigate the effects of long-term valproic acid monotherapy on thyroid function in children with epilepsy and to identify potential risk factors for thyroid hormone imbalance and the development of subclinical hypothyroidism.

Material and methods

This prospective cross-sectional study was conducted at the University Children's Hospital in Belgrade, Serbia, during the period 2011-2014. The study was approved by the Ethics Committee of the University Children's hospital.

Ambulatory patients with epilepsy on VPA monotherapy for at least six months were included in the study. The main inclusion criteria were: good seizure control, normal neurological examination, normal school function (if applicable), and normal cerebral computed tomography or magnetic resonance imaging (if performed). Exclusion criteria were: concomitant treatment with other AEDs or treatment with other AEDs prior to VPA, concomitant diseases (endocrinopathies, liver or kidney diseases, systemic disorders), and clinical suspicion of thyroid dysfunction and family history of thyroid disease. The following data were obtained for all patients: sex, age, seizure type, VPA daily dosage, and duration of therapy. A control group consisted of children from the same geographical area without epilepsy, endocrine problems, or any disease or treatment that could interfere with thyroid function, who visited our outpatient clinic during the same period. Informed consent was obtained from parents of all participants in this study.

Thyroid function tests that included serum levels of TSH, FT3, FT4, thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies (TG-Ab) were performed for all patients and controls. Serum VPA concentration was also measured. Blood samples for measurement of VPA in steady state were taken between 08:00 and 10:00 am after an overnight fast, and analysed immediately. Serum levels of TSH, FT3, FT4, TPO-Ab, and TG-Ab were determined by Chemiluminescent Microparticle Immunoassay-CMIA. ARCHITECT reagent kits 7K63, 7K64, 7K62, 2K46, and 2K47 were used for the analysis, and the limits of detection were 1.0 pg/ml for FT3, 5.148 pmol/l for FT4, 0.0025 μIU/ml for TSH, 0.07 IU/ml for Tg-Ab, and 0.16 IU/ml for TPO-Ab. Serum VPA concentration was assayed using the ARCHITECT iValproic Acid assay (*in vitro* chemiluminescent microparticle immunoassay); the limit of detection was 0.51 μg/ml. Clinical features of potential thyroid dysfunction were evaluated by an endocrinologist.

Data were expressed as mean±SD values. Statistical analysis was performed using PASW 18 (SPSS Inc Chicago, IL). The differences between study and control groups were analysed using Chi-square and Mann-Whitney U test; $p<0.05$ was considered statistically significant. Age, seizure type, VPA treatment duration, daily dosage, and serum concentration were entered into the stepwise logistic regression model to study the independent effect of each risk factor on thyroid hormone levels; the threshold was set at 0.1.

Results

General characteristics

In total, 42 patients were eligible for the study, but one patient lacked parental consent and was therefore not included in the study. The study groups consisted of 41 paediatric patients with epilepsy, aged between 3 and 19 years (VPA group) and 41 sex- and age-matched healthy children (control group), as shown in *table 1* . For all patients included in the study, parental consent was obtained.

Table 1. Characteristics of VPA-treated children and healthy controls.

Characteristics	VPA group (*n*=41) mean±SD (range)	Control group (*n*=41) mean±SD (range)
Number of subjects (male/female)	41 (20/21)	41 (19/22)
Age (years)	9.89±3.99 (3-19)	11.26±4.45 (3-19)
VPA daily dose (mg/kg)	20.54±3.84 (12-30)	-
Total daily dosage (mg)	603.65±207.18 (300-1250)	-
VPA serum concentration (μg/mL)	64.65±15.38 (49.11-109.00)	-
Duration of VPA therapy (years)	2.80±1.96 (0.5-8.0)	-

VPA: valproic acid

Thirty-four children were diagnosed with primary generalized seizures (of whom 26 had epilepsy with convulsions, whereas eight had absence seizures) and seven patients were diagnosed with focal seizures (four had benign focal epilepsy and three developed secondary generalization).

The mean duration of VPA treatment was 2.80±1.96 years. VPA was prescribed at a mean dosage of 20.54±3.84 mg/kg per day, resulting in mean VPA serum levels of 64.65±15.38 μg/ml (reference range: 50-100 μg/ml). Five patients (12%) had serum concentrations slightly below the therapeutic range (49.11-49.95 μg/ml) whereas two patients (5%) had VPA serum levels slightly above the therapeutic range (100.20 and 109.00 μg/ml, respectively). These patients were not excluded from the study because clinical response was good and no side effects of VPA long-term treatment were observed on physical examination and routine laboratory testing.

Thyroid function

TSH levels in the VPA group were higher compared to the control group ($p<0.001$). FT4 concentrations were similar in both groups, whereas FT3 was higher in the VPA group, compared with the controls ($p = 0.01$). TPO-Ab and TG-Ab remained within normal range for all patients and healthy children. Results are shown in *table 2*.

TSH >4 mU/l was found in 14/41 (34%) of the VPA group and in none of the controls. All patients had primary generalized epilepsy. Five children receiving VPA (12.2%) had serum TSH >5 mU/l (range: 5.78-10.79) without clinical signs of thyroid dysfunction. Eight patients with TSH >4 mU/l (57%) had serum FT3 levels above the upper limit for healthy controls (range: 5.35-7.25 pmol/l). Thirteen children on VPA monotherapy (32%) had elevated serum FT3 levels with normal TSH concentration and no clinical signs of thyroid dysfunction. However, although within normal limits, their serum TSH levels were higher than in patients whose serum FT3 was not elevated (3.34±1.18 mU/l *vs.* 2.41±1.48 mU/l; $p< 0.05$).

No difference in serum FT4 levels were found between the VPA group and healthy controls. However, the serum FT4 level in children with elevated FT3 depended on TSH concentration; serum FT4 was lower if TSH was above 4 mU/l (10.94±4.01 pmol/l *vs.* 14.27±1.02 pmol/l; $p<0.05$).

Multivariate analysis

Age, seizure type, VPA daily dosage, VPA serum concentration, and duration of treatment were entered into stepwise logistic regression models to investigate their predictor potentials for TSH and FT3. Duration of VPA treatment was the only predictor of TSH levels ($p = 0.031$; CI: -0.67 to -0.03). A cut-off point was set at four years of VPA treatment. Patients on VPA therapy lasting less than four years (24 patients, 58.5%) had significantly higher levels of TSH compared to patients receiving VPA for longer than four years ($p = 0.022$) and healthy controls ($p<0.001$), as shown in *figure 1* . Moreover, children whose VPA treatment

Table 2. Serum thyroid hormone levels in VPA-treated children and healthy controls (Mann-Whitney U test).

Thyroid hormones	VPA group (*n*=41) mean±SD (range)	Control group (*n*=41) mean±SD (range)	*p* value
FT_3 (pmol/l)	5.30±0.97 (1.54-10.58)	4.50±0.49 (3.39-5.28)	0.01
FT_4 (pmol/l)	13.25±2.48 (4.04-16.67)	13.43±2.15 (4.03-17.03)	ns
TSH (mU/l)	3.47±2.05 (0.85-10.79)	2.03±0.72 (0.75-3.76)	<0.001

FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid-stimulating hormone; VPA: valproic acid; ns: not significant.

lasted less than four years were younger than those receiving VPA for longer than four years (9.3±3.9 *vs.* 12.7±2.9; $p<0.05$), and they had a lower daily dosage of VPA (566±164 mg *vs.* 786±305 mg; $p<0.01$). There were no differences in serum VPA level between these two groups (64.48±14.59 mg/l and 65.48±20.10 mg/l; $p = 0.438$).

We found no significant influence of age, seizure type, drug daily dosage, serum concentration, or duration of treatment on FT3 levels (*figure 2*).

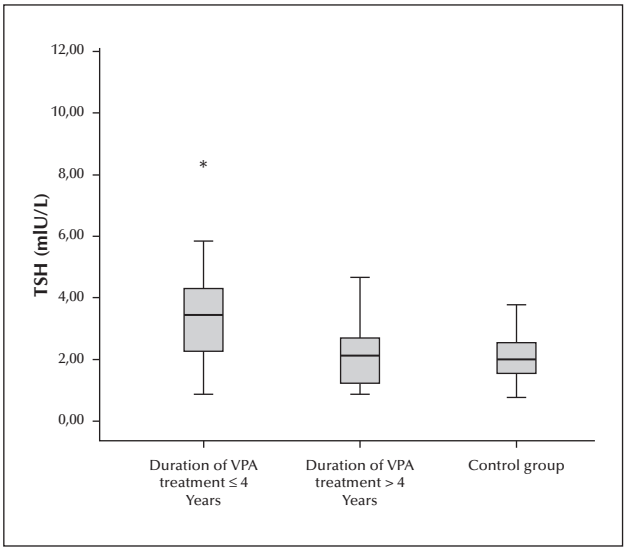

Figure 1. TSH concentration in patients on VPA monotherapy ≤4 years, >4 years, and in the control group. *denotes significant difference ($p<0.001$) in TSH concentration between patients on VPA ≤4 years and the control group.

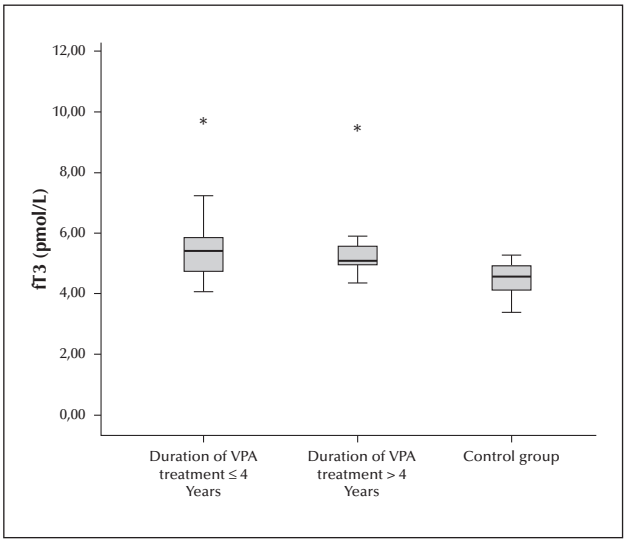

Figure 2. FT3 concentration in patients on VPA monotherapy ≤4 years, > 4years, and in the control group. *denotes significant difference ($p<0.05$) in FT3 concentration between patients on VPA and the control group.

Discussion

The goal of antiepileptic therapy is to control seizures or at least to reduce their number, but the frequency and severity of adverse effects is also a very important issue for clinicians. Several studies have investigated thyroid function in epileptic children during long-term administration of VPA with controversial results. Some authors reported subclinical hypothyroidism in patients on VPA monotherapy, while others found no changes in thyroid hormone balance (Specchio *et al.,* 1985; Caksen *et al.,* 2002; Castro-Gago *et al.,* 2007; Hirfanoglu *et al.,* 2007; Attilakos *et al.,* 2009; Aggarwal *et al.,* 2011; Aygun *et al.,* 2012). It has been suggested that age, duration of VPA treatment, daily dosage, and serum concentration of the drug may impact the effect of VPA on thyroid hormone levels, but the results are controversial.

VPA treatment caused significant increase in the mean level of TSH compared to the control group in our study, which is in agreement with some authors (Specchio *et al.,* 1985; Verrotti *et al.,* 2001; Cansu *et al.,* 2006; Castro-Gago *et al.,* 2007). Elevated serum TSH levels were found in one third of patients on VPA monotherapy, and 12.5% patients exhibited TSH values in the subclinical hypothyroidism range which is less than the 25% reported by other authors (Castro-Gago *et al.,* 2007; Mikati *et al.,* 2007). Consistent with previous reports (Specchio *et al.,* 1985; Cansu *et al.,* 2006), none of our children had increased level of TPO-Ab or Tg-Ab. Therefore, the altered thyroid function in patients on VPA is probably not mediated by the activation of autoimmune mechanisms and increase in TSH levels does not seem to be a compensatory response.

To our knowledge, one study, which included patients on mono and polytherapy with VPA, identified several predictive risk factors for subclinical hypothyroidism: younger age, duration of treatment between 6 and 24 months versus <6 months and >24 months, and VPA polytherapy with enzyme-inducing agents or polytherapy with non-enzyme-inducing agents (Mikati *et al.,* 2007). In contrast, another study revealed duration of VPA treatment for longer than 24 months as a risk factor for subclinical hypothyrodism (Sahu *et al.,* 2012). Our results show that duration of VPA treatment for less than four years may be a risk factor for elevated TSH levels. Moreover, increase in serum TSH during the first year of VPA treatment (Cansu *et al.,* 2006; Attilakos *et al.,* 2009; Aygun *et al.,* 2012; Kafadar *et al.,* 2015), and/or during the first 24 or 36 months of therapy (Tanaka *et al.,* 1987; Sahu *et al.,* 2012), has been reported, in accordance with our results. Nevertheless, some authors reported no effect of length of treatment on TSH levels (Aggarwal *et al.,* 2011; Kim *et al.,* 2012), but their patients

were administered VPA during a shorter period compared to our study.

As mentioned, age (younger than 4 years) has also been reported as a risk factor for development of subclinical hypothyroidism during VPA therapy (Mikati *et al.,* 2007). In contrast, we found no significant correlation between age and TSH level, but we had only one patient younger than 4 years. Nevertheless, it is possible that age may be a confounding risk factor since patients younger than 4 years are more likely to have a shorter duration of VPA treatment compared to older patients. Moreover, other authors also reported no significant impact of age on subclinical hypothyroidism in patients on VPA monotherapy (Castro-Gago *et al.,* 2007; Kim *et al.,* 2012; Sahu *et al.,* 2012).

Significant correlation between TSH levels and VPA daily dose and between subclinical hypothyroidism and high VPA serum concentrations has been reported (Kim *et al.,* 2012). However, our findings are in accordance with other authors who did not find such a correlation and whose VPA serum levels were similar to ours (Castro-Gago *et al.,* 2007; Mikati *et al.,* 2007; Aggarwal *et al.,* 2011).

Serum FT4 concentrations in our study were within the normal range, and this is in agreement with some previously published data (Caksen *et al.,* 2002; Vainionpaa *et al.,* 2004; Verrotti *et al.,* 2009). However, other authors reported serum FT4 to be significantly lower in patients receiving VPA treatment despite their clinically euthyroid status (Specchio *et al.,* 1985; Castro-Gago *et al.,* 2007; Hirfanoglu *et al.,* 2007; Aygun *et al.,* 2012; Doneray *et al.,* 2012; Turan *et al.,* 2014; Yilmaz *et al.,* 2014). Although not below the normal range, our patients with elevated TSH levels had lower FT4 serum levels.

According to some authors, serum FT3 during VPA treatment can remain unchanged (Caksen *et al.,* 2002; Verrotti *et al.,* 2009; Aggarwal *et al.,* 2011; Aygun *et al.,* 2012) or decrease (Eiris-Punal *et al.,* 1999). Our study demonstrated significantly higher serum FT3 in the VPA group, compared to healthy controls. To our knowledge, this finding is coherent with only one earlier report (Castro-Gago *et al.,* 2007). Both elevated serum FT3 and TSH were associated with FT4 levels within a lower normal range. This suggests the possibility of greater conversion of thyroid hormones in the thyroid gland, especially in children whose VPA serum levels are within the higher therapeutic range. Regardless of serum TSH levels, high FT3 was not associated with duration of VPA treatment.

There are, however, some limitations to this study, such as: the relatively small sample size; no baseline level of TSH, FT4 and FT3 in children with newly diagnosed epilepsy before starting VPA monotherapy; and thyroid-function testing performed only once during VPA treatment. However, our results are consistent with prior studies showing alteration of thyroid hormone concentration following VPA monotherapy. We suggest that duration of VPA monotherapy may be a predictor of TSH levels, because children receiving VPA may have elevated serum TSH, especially in the first four years of treatment. Further investigation is necessary to elucidate the relationship between VPA treatment duration and thyroid hormone levels.

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.

We acknowledge the Ministry of Education, Science and Technological Development, Belgrade, Republic of Serbia for support with the project: Experimental and Clinical Pharmacological Investigations of Mechanisms of Drug Action and Interactions in Nervous and Cardiovascular System (No. 175023).

None of the authors have any conflict of interest to declare.

Funding.

The authors received no financial support for the authorship and/or publication of this article. The costs of the research were financed by the Ministry of Education, Science and Technological Development through the project: Experimental and Clinical Pharmacological Investigations of Mechanisms of Drug Action and Interactions in Nervous and Cardiovascular System (No. 175023).

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TEST YOURSELF

(1) Is valproic acid treatment associated with elevated levels of thyroid-stimulating hormone in paediatric patients with epilepsy?

(2) Are gender, valproic acid serum concentration, and duration of valproic acid monotherapy associated with subclinical hypothyroidism in children?

(3) Are levels of free T3 and T4 increased following valproic acid monotherapy in paediatric patients with epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".