

Frequency of Subclinic Hypothyroidism at the Patients That Are Using Valproic Acid

Mehmet Ibrahim Turan¹, Atilla Cayir², Ibrahim Selcuk Esin³, Yasemin Cayir⁴, Huseyin Tan⁵

¹ Department of Pediatric Neurology, Research and Educational Hospital, Diyarbakir, Turkey

² Department of Pediatric Endocrinology, Research and Educational Hospital, Erzurum, Turkey

³ Department of Child Psychiatry, Faculty of Medicine, Ataturk University, Erzurum, Turkey

⁴ Department of Family medicine, Faculty of Medicine, Ataturk University, Erzurum, Turkey

⁵ Department of Pediatric Neurology, Faculty of Medicine, Ataturk University, Erzurum, Turkey

Abstract

Valproic acid is one of the most commonly used anti-epileptics in the treatment of childhood epilepsy. The aim of this study was to determine the risk factors for and incidence of subclinical hypothyroidism (SH) in children with idiopathic epilepsy using valproic acid (VPA). Patients monitored with a diagnosis of idiopathic epilepsy, using valproic acid for longer than 12 months and who were seizure-free for at least 6 months were included in the study. Levels of free thyroxine, free triiodothyronine and thyrotropin were measured. The results were then compared with those of the control group. Rates of SH in patients using VPA and the control group were 18.5% and 6.2%, respectively. The difference was statistically significant ($P < 0.01$). SH was not correlated with age or dose of drug used ($P > 0.01$). In conclusion, SH is a common effect seen in children with epilepsy using VPA. It will be beneficial to measure thyroid functions at specific intervals.

Key Words: Child, epilepsy, Valproic acid, hypothyroidism

(Rec.Date: Aug 12, 2013 Accept Date: Sep 04, 2013)

Corresponding Author: Dr. Mehmet Ibrahim Turan, Department of Pediatric Neurology, Research and Educational Hospital, Diyarbakir, Turkey 21070.

Fax: +90 412 236 10 14, **Tel :** +90 505 2604621

E-mail: turan78tr@hotmail.com

Introduction

Subclinical hypothyroidism (SH) is a common and self-limiting thyroid function disorder that can be seen in childhood. Treatment is not generally required, although it is recommended in the presence of a chronic disease or if the patient is symptomatic [1]. SH is defined as thyroid stimulant hormone levels being higher than the reference level while free thyroxine (FT4) is at normal level (euthyroid). As SH is an early predictor of further thyroidal function disorders, early diagnosis and follow-up are important [2]. Thyroid functions are affected by non-endocrinal disorders, although the mechanisms involved are not clear [3-7].

Valproic acid (VPA), the effects of which on thyroid functions were evaluated in this study, is an anti-epileptic drug with a broad spectrum of activity [8]. It is thought to function by blocking voltage-dependant sodium channels [9]. It is one of the most commonly used anti-epileptics in childhood [10]. As VPA is used for prolonged periods in the management of seizures, it is important to monitor patients in terms of potential adverse effects. Several studies have investigated the adverse events involved with VPA, of which metabolic and endocrine abnormalities are especially important [11]. While studies have investigated the effect of VPA on thyroid functions, the relationship between them cannot be defined clearly. Some studies have reported that VPA has a negative on thyroid functions, while others have failed to identify such an effect [12, 13].

This study investigated the effect of VPA, a commonly used anti-epileptic in the management of childhood epilepsy, on thyroid function test results and the emergence of SH in long-term use.

Material and Methods

This study was performed at the division of Pediatric Neurology, Department of Pediatrics at the Ataturk University Faculty of Medicine, Turkey. Informed consent was obtained from the parents of all children enrolled. The study was approved by the local Ethical Committee.

The study group consisted of 124 ambulatory children under monitoring for epilepsy and 136 healthy children. The children in the study group suffered from different types of idiopathic epilepsy. Diagnosis of epilepsy was based on electroencephalography and clinical features.

None of the patients received any medication other than an antiepileptic drug. VPA was prescribed at the normal dosages, twice daily. No other drugs were prescribed. Children were deemed eligible for inclusion if they were aged 2 to 15 years, had received valproate monotherapy for 12 months or longer, and had been seizure-free for 6 months or longer.

The patients and healthy subjects shared the same parameters. Sex and age-matched children were selected as controls. The children in the control group were admitted to the pediatric outpatient clinic for reasons other than systemic problems. Controls were similar to patients except for epilepsy and receipt of valproate therapy. We viewed the records of all patients and considered the following details: age at onset, length of drug use, drug dosage and laboratory parameters including free triiodothyronine (FT3), free thyroxine (FT4) and thyrotropin (TSH).

In accordance with laboratory reference values, normal serum values were determined at 0.35-4.94 μ IU/L for TSH, 0.93-1.7 ng/dl for FT4 and 1.8-4.6 pg/mL for FT3. While TSH levels were higher than 4.94 μ IU/L in cases with SH, FT4 values remained within normal limits.

Exclusion criteria were use of any medications known to interfere with liver, renal or thyroid functions, thyroid, kidney or liver disease, endocrine disorders and abnormal neurological examination or cerebral computed tomography and/or magnetic resonance imaging scan.

Blood samples were collected at least 12 months after start of VPA therapy, between 8:00 and 10:00 a.m. after 12-h fasting in order to avoid diurnal variations.

All blood samples were stored at -80 °C until analysis. All tests were performed according to the manufacturer's instructions. Serum FT3 (pg/mL), FT4 (μ g/dL) and TSH (μ l U/L) were determined in serum using electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, D-68298, Germany).

Statistical Analysis

Data were subjected to Pearson's chi-square test using Statistical Package for Social Sciences 18.0 (Armonk, NY, USA) software. Significance was set at $p \leq 0.001$. Results are expressed as mean $\pm$ standard deviation.

Results

The study group consisted of 65 (52.4%) male and 59 (47.6%) female patients, and the control group of 68 (52.3%) male and 62 (47.7%) female children. Mean age was 7.91 ± 3.7 in the study group and 7.97 ± 4 in the control group. There were no statistically significant differences between the two groups in terms of sex and age ($P > 0.05$).

Mean duration of drug use in the VPA group was 16.9 ± 4.5 (12-24) months, with a mean dosage of 21.4 ± 4.4 (15 - 40) mg/kg.

Measured levels in the VPA group were FT3, 4.12 ± 0.68 (2.35 – 5.49) pg/mL, FT4, 1.26 ± 1.14 (0.94 - 1.56) $\mu\text{g/dL}$ and TSH, 3.48 ± 1.49 (1.04 – 8.34) $\mu\text{l U/L}$. In the control group, the measured levels were FT3, 4.17 ± 0.59 (2.97 -5.4) pg/mL, FT4: 1.34 ± 0.15 (0.86 - 1.7) $\mu\text{g/dL}$ and TSH: 2.49 ± 1.25 (0.75 – 6.94) $\mu\text{l U/L}$.

Statistically significant differences were detected in terms of SH between the VPA and control groups (Table 1).

No linear correlation was determined between SH and age in the VPA group ($r=0.078$, $P=0.392$). There was also no significant correlation between the presence of SH and dose of drug used in the VPA group ($r = 0.154$, $P = 0.087$).

Table 1. Rate of subclinical hypothyroidism in the VPA and control groups

Groups	SH (+)	SH(-)	P value
	No. (%)	No. (%)	
VPA	23 (18.5%)	101 (81.5%)	0.003*
Control	8 (6.2%)	122 (93.8%)	

Note: Pearson chi-square test was performed. VPA, valproic acid; SH, subclinical hypothyroidism; No. patient number.

* $P \leq 0.01$ regarded as significant.

Discussion

This study determined a statistically higher incidence of SH in children using VPA after at least 12 months of drug use compared to the control group. The association between VPA and SH is not clear [13]. One recent study reported that the risk of SH increases significantly with VPA use longer than 6 months and that the risk increases still further the lower the age of the patient [12]. However, Sahu et al. showed that the risk of SH emerging is not related to age or dosage [14]. Similarly, the data from this study revealed no relationship between risk of SH emerging and age or dosage. One hypothesis suggested in patients using VPA is the inhibition of somatostatine, an important inhibitor of secretion of TSH via stimulation of gamma amino butyric acid (GABA), by VPA [15]. On the other hand, it has also been suggested that selenium and zinc deficiency, which is commonly seen in patients using VPA, is related to SH [16]. These hypotheses are supported by publications reporting an increased frequency of SH in patients with Down syndrome who also have zinc deficiency and suggesting that selenium deficiency reduces the synthesis of thyroid hormones [17, 18].

Thyroid hormones are affected by many systemic diseases [19, 20]. Clinical hypothyroidism can be seen later in children with SH [21]. Therefore, all adolescents and children that are euthyroid or have SH should be monitored at specific in terms of their thyroid functions [22]. TRH assays also can be helpful in SH cases [23].

The main limitation of our study is the lack of baseline TSH, FT4 and FT3 values for the enrolled patients before VPA therapy started. Other limiting factors are that blood samples could only be taken once, for ethical reasons, and lack of re-evaluation of thyroid hormone levels after the drug was stopped.

In conclusion, SH is a common effect in children using VPA for the management of epilepsy. As VPA exhibits an effect on thyroid hormones independent of age and dosage, we suggest that it will be beneficial to measure the levels of thyroidal hormones periodically in children using VPA.

References

1. Bona G, Prodam F, Monzani A. Subclinical hypothyroidism in children: Natural history and when to treat. *J Clin Res Pediatr Endocrinol*. 2013;5 Suppl 1:23-8.
2. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: Scientific review and guidelines for diagnosis and management. *Jama*. 2004;291(2):228-38.
3. Demirkaya M, Sevinir B, Saglam H, Ozkan L, Akaci O. Thyroid functions in long-term survivors of pediatric hodgkin's lymphoma treated with chemotherapy and radiotherapy. *J Clin Res Pediatr Endocrinol*. 2011;3(2):89-94.
4. Hassan S, Qureshi W, Donthireddy V, Kuriakose P. Congenital von willebrand's disease and clinical hypothyroidism. *Haemophilia*. 2013;19(2):242-5.
5. Yan Z, Fan K, Fan Y, Wang X, Mao Q, Deng G, Wang Y. Thyroid dysfunction in chinese patients with chronic hepatitis c treated with interferon alpha: Incidence, long-term outcome and predictive factors. *Hepat Mon*. 2012;12(9):e6390.
6. Cetinkaya S, Kendirci HN, Agladioglu SY, Bas VN, Ozdemir S, Bozkurt C, Aycan Z. Hypothyroidism due to hepatic hemangioendothelioma: A case report. *J Clin Res Pediatr Endocrinol*. 2010;2(3):126-30.
7. Kosova F, Cetin B, Akinci M, Aslan S, Seki A, Pirhan Y, Ari Z. Serum copper levels in benign and malignant thyroid diseases. *Bratisl Lek Listy*. 2012;113(12):718-20.
8. Rylance GW. Treatment of epilepsy and febrile convulsions in children. *Lancet*. 1990;336(8713):488-91.
9. Perucca E. The new generation of antiepileptic drugs: Advantages and disadvantages. *Br J Clin Pharmacol*. 1996;42(5):531-43.
10. Beydoun A, D'Souza J. Treatment of idiopathic generalized epilepsy - a review of the evidence. *Expert Opin Pharmacother*. 2012;13(9):1283-98.
11. Verrotti A, la Torre R, Trotta D, Mohn A, Chiarelli F. Valproate-induced insulin resistance and obesity in children. *Horm Res*. 2009;71(3):125-31.
12. Mikati MA, Tarabay H, Khalil A, Rahi AC, El Banna D, Najjar S. Risk factors for development of subclinical hypothyroidism during valproic acid therapy. *J Pediatr*. 2007;151(2):178-81.
13. Verrotti A, Laus M, Scardapane A, Franzoni E, Chiarelli F. Thyroid hormones in children with epilepsy during long-term administration of carbamazepine and valproate. *Eur J Endocrinol*. 2009;160(1):81-6.
14. Sahu JK, Gulati S, Kabra M, Arya R, Sharma R, Gupta N, Kaleekal T, Reeta K, Gupta YK. Evaluation of subclinical hypothyroidism in ambulatory children with controlled epilepsy on valproate monotherapy. *J Child Neurol*. 2012;27(5):594-7.
15. Loscher W, Schmidt D. Increase of human plasma gaba by sodium valproate. *Epilepsia*. 1980;21(6):611-5.

16. Graf WD, Oleinik OE, Glauser TA, Maertens P, Eder DN, Pippenger CE. Altered antioxidant enzyme activities in children with a serious adverse experience related to valproic acid therapy. *Neuropediatrics*. 1998;29(4):195-201.
17. Pizzulli A, Ranjbar A. Selenium deficiency and hypothyroidism: A new etiology in the differential diagnosis of hypothyroidism in children. *Biol Trace Elem Res*. 2000;77(3):199-208.
18. Bucci I, Napolitano G, Giuliani C, Lio S, Minnucci A, Di Giacomo F, Calabrese G, Sabatino G, Palka G, Monaco F. Zinc sulfate supplementation improves thyroid function in hypozincemic down children. *Biol Trace Elem Res*. 1999;67(3):257-68.
19. Tarim O. Thyroid hormones and growth in health and disease. *J Clin Res Pediatr Endocrinol*. 2011;3(2):51-5.
20. Ergur AT, Taner Y, Ata E, Melek E, Bakar EE, Sancak T. Neurocognitive functions in children and adolescents with subclinical hypothyroidism. *J Clin Res Pediatr Endocrinol*. 2012;4(1):21-4.
21. Radetti G, Gottardi E, Bona G, Corrias A, Salardi S, Loche S. The natural history of euthyroid hashimoto's thyroiditis in children. *J Pediatr*. 2006;149(6):827-32.
22. Ozen S, Berk O, Simsek DG, Darcan S. Clinical course of hashimoto's thyroiditis and effects of levothyroxine therapy on the clinical course of the disease in children and adolescents. *J Clin Res Pediatr Endocrinol*. 2011;3(4):192-7.
23. Ergur AT, Evliyaoglu O, Siklar Z, Bilir P, Ocal G, Berberoglu M. Evaluation of thyroid functions with respect to iodine status and trh test in chronic autoimmune thyroiditis. *J Clin Res Pediatr Endocrinol*. 2011;3(1):18-21.