SUBCLINICAL HYPOTHYROIDISM AND VALPROIC ACID TREATMENT IN CHILDREN WITH EPILEPSY

Diana EPURE[1]
Mărgărita MATEI[2]
Smaranda NIȚĂ[3]
Magda SANDU[4]
Daniel TELEANU[5]
Raluca TELEANU[6]

ABSTRACT:
THERE HAVE BEEN CONFLICTING REPORTS ON THE POSSIBLE ROLE OF VALPROIC ACID TREATMENT IN CHILDREN WITH EPILEPSY ON THE THYROID FUNCTION, WITH SOME STUDIES ASCRIBING SUBCLINICAL HYPOTHYROIDISM AS A POSSIBLE SIDE EFFECT OF THE DRUG.
IN THIS ARTICLE, WE GATHERED DATA REGARDING THYROID FUNCTION ON OUR PATIENTS TREATED WITH VALPROIC ACID, WHILE ALSO DESCRIBING THE TYPES OF SEIZURES ENCOUNTERED, THE DURATION OF TREATMENT AND THE VARIOUS LESIONS UNDERLYING THE EPILEPTIC SEIZURES.

KEY WORDS: VALPROIC ACID, HYPOTHYROIDISM, EPILEPSY, CHILD

INTRODUCTION

Valproic acid (VPA) is one of the most effective broad-spectrum and extensively used antiepileptic drugs available for treatment of both generalized and partial epilepsies in children. The most recognized adverse reactions encountered in VPA therapy are hepatotoxicity, thrombocytopenia and other hematological abnormalities as well as weight gain, the latter especially affecting female patients. Additionally, dysmenorrhoea and amenorrhoea in women treated with VPA are well documented side effects. Despite previously negative correlations between VPA therapy and subclinical hypothyroidism in

[1] MD Department of Pediatric Neurology, "Dr. Victor Gomoiu" Children's Hospital, Bucharest, Romania
[2] MD Endocrinoloy, "Dr. Victor Gomoiu" Children's Hospital, Bucharest, Romania
[3]MD, Department of Pediatric Neurology, "Dr. Victor Gomoiu" Children's Hospital, Bucharest, Romania
[4] PhD MD "Carol Davila" University of Medicine, Bucharest
[5] PhD MD "Carol Davila" University of Medicine, Bucharest
[6] Assoc. Prof. MD, PhD, "Carol Davila" University of Medicine, Bucharest, ralucate@gmail.com

children, an rising number of studies show contrasting results, leaving room for possible implementation of screening programs for evaluation of thyroid function in children undergoing anticonvulsant therapy with VPA.

The pathways of thyroid hormone synthesis, secretion, transport throughout the body and metabolism offer many sites of drug interaction. Currently, testing for thyroid function is common in clinical practice, as a wide range of medication is already known to affect it. The thyroid profile studied included measurements of triiodothyronine (T3), thyroxine (T4), free T4 (FT4), basal thyroid-stimulating hormone (TSH) as well as stimulated TSH (post - administration of thyrotropin releasing hormone - TRH). TSH, secreted by the thyrotrope cells of the anterior pituitary is of maximal importance in the regulation of the thyroid axis and constitutes the best indicator of thyroid function in clinical practice, because of its high sensitivity to changes in serum thyroid hormone levels. Subclinical hypothyroidism refers to elevated levels of plasma TSH while plasma levels of thyroid hormones, T3 and T4, stand within normal limits.

Antiepileptic drugs such as Carbamazepine, Phenobarbital and Phenytoin have been cited to alter the levels of thyroid hormones, by interfering with their hepatic metabolic pathways, namely causing induction of microsomal enzyme systems. VPA is metabolized in the liver via glucuronide conjugation and oxidation, as are, to a small extent, T3 and T4. However, there are contrasting results in clinical trials carried, in different conditions, throughout the years, on the possible role of VPA in affecting the thyroid function, in children. While various studies point to no effect of VPA on the thyroid function, a number of clinical trials found significant alterations of plasma TSH levels following long-term administration, accounting for subclinical hypothyroidism. Moreover, some studies cite the same effect after relatively short periods of time following initiation of VPA therapy. It should be noted that, on most occasions, discontinuation of VPA therapy led to normalization of the thyroid parameters.

This study presents the results of studying the thyroid function in children receiving VPA for various forms of epilepsy.

SUBJECTS AND METHODS

We gathered data on 136 children, aged 1 to 19 years, with epilepsy, receiving valproate therapy admitted in the Department of Pediatric Neurology of "Dr. Victor Gomoiu" Children's Hospital, Bucharest, Romania. The patients were excluded if they had a personal or family history of hypothyroidism or endocrine dysfunction or if they had any cerebral lesions involving the hypothalamo - hypophyseal tract.

The type of seizures encountered were classified according to the International League Against Epilepsy and age at onset. Frequency of clinical manifestations and duration of antiepileptic treatment were noted. The patients had performed a cerebral imagistic investigation (cerebral MRI). A part of the patients were on a combination of antiepileptic drugs including VPA and they underwent a periodical analysis of the plasmatic level of valproate.

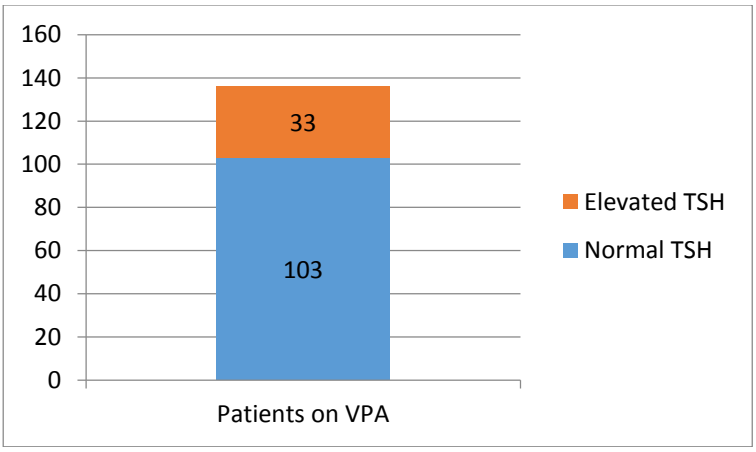
The thyroid function was assessed by determining serum levels of TSH and free T4.

RESULTS

33 patients (24%) aged 3 to 19, had elevations of the plasmatic level of TSH, with free T4 situated in the normal range of values, accounting for subclinical hypothyroidism (Figure 1). The patients had been on VPA treatment for different periods of time. The

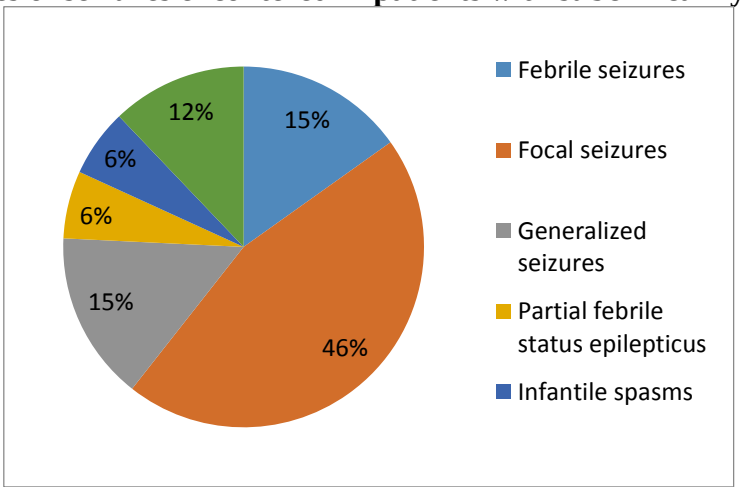
largest period of time spent on VPA therapy was 17 years, with thyroid function being assessed and subclinical thyroidism found after 15 years of treatment. The smallest period of time spent on VPA therapy was 4 months, with subclinical hypothyroidism being diagnosed within one month since the initiation of treatment. The average time spent on VPA therapy until the presence of subclinical hypothyroidism was 31,65 months.

Figure 1. Distribution of total number of patients with normal versus elevated TSH values



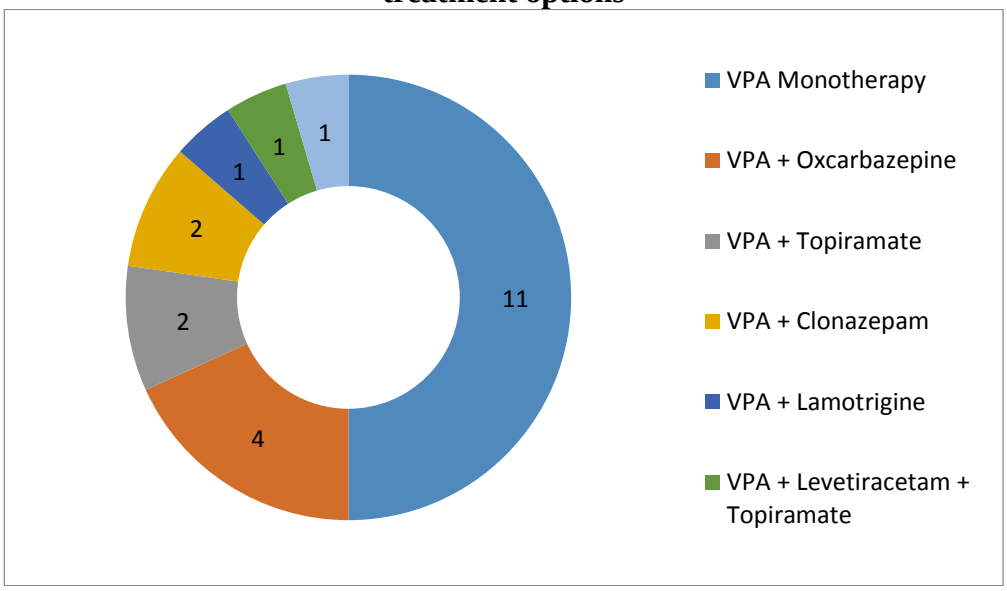
A number of 11 patients had a history of perinatal incidents and 13 patients had cerebral lesions, as assessed by cerebral MRI. One patient had been diagnosed with Angelman syndrome and had polymorphic seizures. 7 patients had febrile seizures, of which two had a partial febrile status epilepticus. 15 patients had afebrile focal seizures while 4 patients showed generalized seizures (Figure 2). Two patients had West syndrome, one of them suffering from tuberous sclerosis, while the other one had cerebral lesions accounting for perinatal hypoxic - ischemic encephalopathy. One patient had type I neurofibromatosis.

Figure 2. Types of seizures encontered in patients with subclinical hypothyroidism



Apart from VPA, a number of 12 patients were on antiepileptic polytherapy, the added treatment choices being oxcarbazepine, topiramate, levetiracetam, clobazam and clonazepam (Figure 3).

Figure 3 Distribution of patients with subclinical hypothyroidism according to treatment options



CONCLUSIONS

Despite being a widely used and already extensively studied antiepileptic drug, the increasingly positive correlations between VPA therapy in children with epilepsy and induction of subclinical hypothyroidism, as well as the relatively scarce information on the mechanisms involved, suggest that more attention should be paid to the implementation of standard thyroid tests to aid in prospective studies.

In this article, we aimed to present our data regarding the presence of subclinical hypothyroidism in a heterogenous set of patients with different forms of epilepsy, undergoing VPA treatment in monotherapy or associated with other antiepileptic drugs.

In the future, our goal is to gather children undergoing valproate monotherapy into a prospective study, in order to better study the correlation between valproate and subclinical hypothyroidism in children.

REFERENCES

1. **Attilakos A, Katsarou E, Prassouli A, Mastroyianni S, Voudris K, Fotinou A, Garoufi A.** Thyroid function in children with epilepsy treated with sodium valproate monotherapy: a prospective study, *Clinical Neuropharmacololgy* 2009 Jan-Feb;32(1):32-4.
2. **Caksen H, Dülger H, Cesur Y, Odabaş D, Tuncer O, Ataş B**. No effect of long-term valproate therapy on thyroid and parathyroid functions in children, *International Journal of Neuroscience.* 2002 Nov;112(11):1371-4.
3. **Cansu A, Serdaroğlu A, Camurdan O, Hirfanoğlu T, Bideci A, Gücüyener K.** The evaluation of thyroid functions, thyroid antibodies, and thyroid volumes in children with epilepsy during short-term administration of oxcarbazepine and valproate, *Epilepsia*. 2006 Nov;47(11):1855-9.
4. **Eirís-Puñal J, Del Río-Garma M, Del Río-Garma MC, Lojo-Rocamonde S, Novo-Rodríguez I, Castro-Gago M**. Long-term treatment of children with epilepsy with valproate or carbamazepine may cause subclinical hypothyroidism,*Epilepsia*. 1999 Dec;40(12):1761-6.
5. **Hirfanoglu T, Serdaroglu A, Camurdan O, Cansu A, Bideci A, Cinaz P, Gucuyener K.** Thyroid function and volume in epileptic children using carbamazepine, oxcarbazepine and valproate, *Pediatrics International,* 2007 Dec;49(6):822-6.
6. **Isojärvi JI, Pakarinen AJ, Myllylä VV**. Thyroid function with antiepileptic drugs,*Epilepsia*. 1992 Jan-Feb;33(1):142-8.
7. **Sahu J.K., Gulati S., Kabra M., Arya R., Sharma R., Gupta N., Kaleekal T., Reeta K., Gupta Y.K.** -Evaluation of Subclinical Hypothyroidism in Ambulatory Children with Controlled Epilepsy on Valproate Monotherapy, *Journal of Child Neurology* 2012 27: 595
8. **Verroti A., Laus M., Scardapane A., Franzoni E., Chiarelli F**. Thyroid hormones in children with epilepsy during long - term administration of carbamazepine and valproate, *European Journal of Endocrinology*, 2009 160 81-86