

THE INFLUENCE OF THE TREATMENT WITH VALPROIC ACID IN THE THYROID FUNCTION IN CHILDREN AND ADOLESCENTS DIANGNOSTICATED WITH EPILEPSY

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Abstract

Some of the children who have been diagnosed with epilepsy and treated with valproic acid presented an alteration of the thyroid function (subclinical hypothyroidism).

Key words: epilepsy, valproic acid, thyroid function

Introduction

The hypothyroidism is the most frequent anomaly of the thyroid function in children, and in the majority of the times it is caused by the chronic autoimmune thyroiditis (1). Besides primary and central, the hypothyroidism can be subclinical (levels raised blood of thyrotropin [TSH] and normal levels of thyroxin [T4]) or clinical (TSH's high concentration in whey and fall of T4).

The thyroid function is regulated as much for retroaction negative (feedback) as for self regulation, being related intimately to the quantity of iodine of the organism. The biological action is not realized by the hormones tied to the proteins but only the free fraction.

The subclinical hypothyroidism can lead to an evident hypothyroidism. This disease cannot be identified on the basis of symptoms or specific signs and for this only it is possible to diagnose using the laboratory tests. Whatever the reason being, the hypothyroidism in children can have harmful effects on the growth, school yield and the pubertal development.

Clinically, it appears with decrease of the speed of the growth with a low resultant stature, alteration of the school yield, weakness and lethargy, intolerance to the cold, constipation, skin dries, fragile hair, facial inflammation and muscles pain, delay in the pubertal development. The secretion of hormone of the growth can be normal or diminished and the production of the factor of growth type insulin 1 is in general diminished (1).

The diagnosis puts in relation to the blood levels. The first one generally confirms the presence of hypothyroidism, whereas the second help to distinguishing between primary,

secondary or tertiary disease. In case of hypothyroidism the treatment of election is the substitution for T4.

The valproate (VPA), sodium salt of the valproic acid or the dipropilacetic acid, is, together with the phenytoin, the phenobarbital and the carbamecepine, one of the 4 of anti-epileptic drugs called "classics" or "majors". It is a question of an anti-epileptic of very wide spectrum, assets opposite to practically all kinds of crisis, of remarkable efficiency and of excellent tolerance the majority of the times. The affectation on the cognitive functions has been demonstrated minim or practically void, which has been a point to favor for the utilization in children and teenagers. Unlike the medicaments mentioned above it behaves as an enzymatic inhibitor.

A more detailed description of its properties, indications and adverse effects they are available in the prospectus and in the technical sheet (2, 3).

There is not known with accuracy the mechanism of action of the valproic acid, but part of VPA effect is related to a direct or secondary increase of the concentrations of the inhibiting neurotransmitter GABA (gammaaminobutiric acid), caused possibly by a decrease of the metabolism or by a decrease in his recaptation.

The results of several works seem to suggest that the treatment with VPA can have an effect in the thyroid function fundamentally appearing like subclinical hypothyroidism. This effect seems to be related according to some works with the time of administration, according to others with the thyroid previous function of the patient. Other works think that this effect does not seem to be attributable directly to the VPA therapy, but this one would promote the effect of other medicaments on the thyroid function on having administered them in polytherapy. In any case, the majority of authors find reasonably to recommend the accomplishment of controls of thyroid function before and during the treatment at least in patients of risk. Nevertheless, the population of risk is far from being well definite.

Objectives

Today it is not yet known exactly with what frequency there happens the alteration of the thyroid function in patient children and epileptic teenagers in treatment with VPA, and what consequences this aspect could have. Of equal way, the magnitude of the problem is known but it can be important because the enormous prevalence of the epilepsy to this age and so frequent use of the VPA in this population (1).

Knowing this information is fundamental to know what type of controls could be indicated, in what population and in what moment. At present there are not existing clear recommendations. In the habitual practice the majority of neuropediatrics realizes an analytical blood exam before initiating the treatment and another control sometime after beginning the treatment with valproic acid, with the object fundamentally to discard an effect on the hepatic function. In view of the current condition of knowledge it brings over of the possible effect on the thyroid, we could question these recommendations.

The present work has as aim to analyze the influence of the treatment with VPA on the thyroid function in children and teenagers with epilepsy, describe which is the effect that takes place (is produced), with what frequency it happens and on what variables seems to depend, in order to be able to establish if it is possible a series of recommendations or indications of screening and of treatment.

Material and methods

The present work is an observational, retrospectively and descriptively study of a series of cases of children and teenagers with epilepsy who receive treatment with VPA and to which they have been done a determination of thyroid hormones.

The criteria of selection have been therefore a population with age included between 0 and 18 years, in anticonvulsive treatment with VPA during the previous year, to which there has been realized a determination of thyroid hormones. There have not been included in the study patient that were presenting before alterations of the thyroid function.

The source of information was the clinical histories gathered from the service of Pediatrics of the Clinical Hospital San Carlos of Madrid, concretely in Neuropediatrics consultation. The thyroid function is valued initially across the blood levels of the thyroid hormones (T3, T4, TSH), previous informed consent signed by the parents.

Some patients are included thanks to the serum levels of valproic acid registered in the computer system of clinical analyses of the Clinical Hospital San Carlos from January 1, 2006 until December 31, 2007, being established the contact with them after identification.

There have been gathered demographic information, indication of the anticonvulsive treatment, age at the beginning of the disease, age in the moment of the withdrawal of the information, the base disease, the dose of

VPA (usually 15-45mg/kg/dia in two or three captures) and the blood levels of the medicine, the duration of the treatment, analytical information and concomitant diseases of the patient as well as the capture of other anticonvulsive drugs.

The analytical information that has been considered available has been the last found in the clinical history of the patients. The serum levels of valproic acid have been considered between 20 and 40 mg/kgc/day and in case of the TSH, according to the laboratory of clinical analyses of the Clinical Hospital San Carlos, between 0.34 and 5.6 mU/l.

In case of be confirming the presence of a biochemical hypothyroidism, they have been sent to the consultation of endocrinology to extend study. The clinical and analytical information suggesting of thyroid dysfunction was considered to be a complication of the treatment.

As for the statistical analysis, the qualitative variables appear with his distribution of frequencies. The quantitative variables are summarized with his average and standard diversion. The association between qualitative variables was evaluated with the test of *Chi – square Table or Fisher' test*, in case more than 25 % of the awaited ones were minor of 5. For all the tests there was accepted a value of significance of 5 %. The processing and analysis of the information was realized by means of the statistical package SPSS 12.0.

Results

The number of the patients included in the study was of 23 patients. The middle ages of the studied group are of 9.00 years, with a maximum of 18 and one minimum of 1 (standard deviation 5.931). They are women 52.2 % and men 47.8 %.

The majority of patients followed in the consultation were recounting history of some type of convulsions. The final indication of treatment with VPA has been epilepsy (without specifying type) in 21 patients (91.30 %) and neonatal convulsions in 2 (7.70 %).

The doses of VPA are comprehended between 17.2 and 35.7 mg/Kg/day (average 26.45 mg/kg/day) in 2 ó 3 doses oral way.

The valproic acid, according to the blood levels recounted above like therapeutic for this indication, is inside the therapeutic range in 20 of the patients (92 %) and is in subtherapeutic range in 3 (8.00 %). None of the patients was presenting overdose of dose of valproic acid.

It has been found an increase of the serum levels of TSH in 7 of 23 patients (30.43 %), between 5.85 and 9.24 mUI/L (1 appears). This relation seems to be present as much in the cases that receive polytherapy (figure 1) as in that they receive monotherapy with valproic acid (figure 3).

It has not been found statistically significant differences between the age and the sex regarding to the existence of TSH's level increase.

The children with hormonal alterations have been sent to endocrinology section for study. Actually it is depending on results.

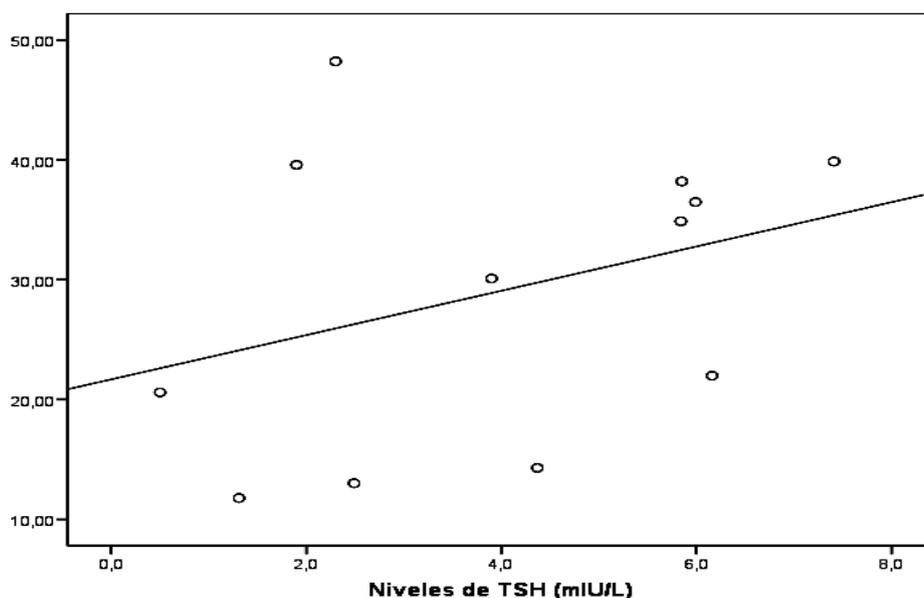


Fig 1. TSH levels in the cases that receive polytherapy.

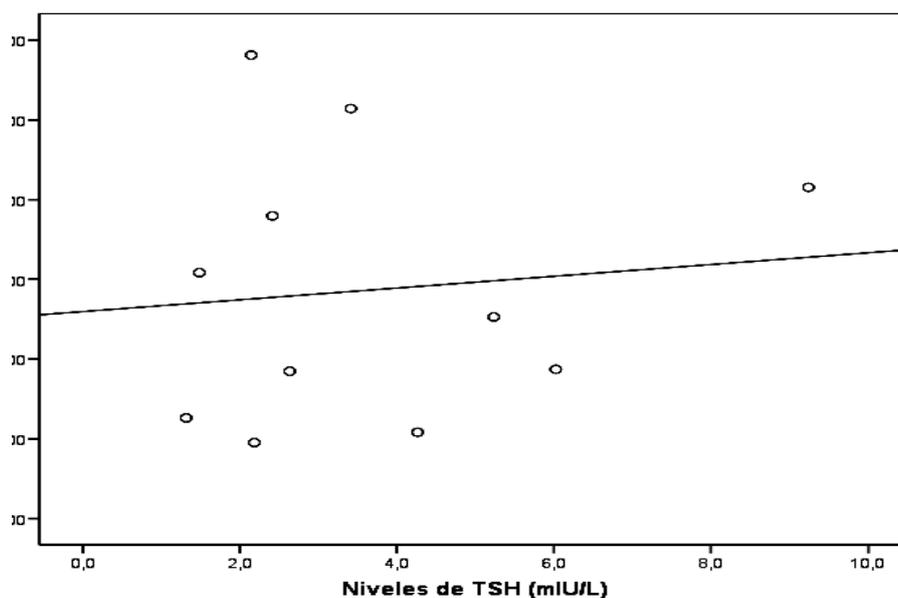


Fig 2. TSH levels in the cases that receive monotherapy with valproic acid.

Discussions

The use of the oral therapy (principally valproic acid) has improved the forecast of the patients with epileptic disease, besides offering a comfort in the daily life of these. A correct anti-epileptic therapy prepares the neurological deterioration, and this is furthermore importantly in the age of development.

The valproic acid is at present the anticonvulsivant more frequently used in children and teenagers in developed countries. To have it, there was contributing, as we already we've been commented, a lot of factors, as the efficiency, his wide spectrum, his availability in different forms and pharmaceutical presentations, his excellent tolerance, with practically absence of sedative action or effects on the cognition, and his safety.

As regards the safety and the appearance of adverse effects, such and so it comes recounted in the technical sheet and the prospectus of the medicament, classically it has given attention to the effects of the valproic acid on the hepatic function, especially in those patients of minor age. Having this intention, and in spite of the absence of clear recommendations, the neuropediatrics use to realize an analytical blood exam, the first before and another a little time after initiating the treatment, controlling also the platelets, the times of coagulation, the amylase and, in occasions, the amonio. Nevertheless, it is not habitual any type of control of the thyroid function in absence of symptoms.

According to the information of the present study, an intrinsic relation exists between the appearance of the hypothyroidism and the treatment with valproic, both in monotherapy and in polytherapy (valproic acid more than others antiepileptic drugs). This information rests those already aimed on other works.

It is not known any information about the magnitude of the possible problem, though having in our mind the distribution bimodal of the incidence/frequency of the epilepsy, with a peak in pediatric age, and the preferential indication of the valproic acid, as it has been explained, to these ages, is of supposing that it can be important.

Other authors have proposed that would be reasonable to realize controls of thyroid function before and during the treatment with VPA. Nevertheless, there is no information on in what patients' subgroups, in what moments and for what period of time would be necessary to realize the above mentioned controls.

In order to give response to all these questions, and in view of the results of this work and of others of the literature that show a relation between the treatment with valproic acid and the appearance of subclinical hypothyroidism in children and teenagers with epilepsy, it is necessary to realize prospective controlled studies that should allow to clarify, first, the presence of a causal relation and, secondly, to sit the bases to establish a few recommendations to detect and to treat precocious and adequately this condition in the clinical practice.

Conclusions

- There is observed a relation between the treatment with VPA in children and teenagers with epilepsy and the appearance of alterations of the thyroid function in the shape of subclinical hypothyroidism.
- The occurrence of these alterations is observed in this academic work in children and teenagers with epilepsy in treatment with valproic acid both in monotherapy and in polytherapy, independently of the age and of the sex.
- The frequency of these alterations, the variables on which depends as well as the causality of these observations show that in the next future should be necessary the accomplishment of other prospective controlled studies.
- At the moment there is no sufficient information to give us the ability to make some recommendations concerning the indication of a control of the hormonal function in children and teenagers with epilepsy in treatment with VPA neither what moment, in case it should be considered to be indicated, could be more ideal this accomplishment.

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