RESEARCH ARTICLE

CHANGING IN THYROID FUNCTION TEST IN CHILDREN UNDERWENT ANTIEPILEPTIC THERAPY

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Abstract

Objective

To determine the changes in thyroid function tests in children who underwent antiepileptic therapy in Shahid Beheshti Hospital, Kashan, in 2008.

Materials & Methods

This analytical-observational study was carried out in a cohort fashion without an external control group (self controlled) on 45 children with new onset epilepsy who had not been previously treated with antiepileptic medications. Three subjects were excluded from the study because of presenting clinical symptoms of hypothyroidism. Plasma levels of TSH, T3, FT3, T4 and FT4 hormones were measured and compared at baseline and 3 and 6 months after treatment.

Results

The results of Mann-Whitney statistical analysis suggested that the increase in the plasma level of TSH was significant only in the Sodium Valproate group. The plasma level of T3 significantly decreased 3 and 6 months after treatment in the Phenobarbital group while the plasma level of FT3 significantly decreased only in the Sodium Valproate group. The decrease in T4 plasma level was significant in all groups (Carbamazepine group, Sodium Valproate group and Phenobarbital group) 3 and 6 months after the onset of treatment but the decreasing in FT4 plasma level was only significant in the Carbamazepine group 6 months after the commencement of treatment.

Conclusion

Phenobarbital had the least effect on thyroid hormones. Considering the effect of such medications on thyroid function tests, it seems necessary to check the plasma levels of hormones periodically after beginning the treatment.

Key words: Epilepsy,Children,Thyroid Function Tests

Introduction

Seizure is a sudden change in motor and/or behavioral activity with a limited duration due to abnormal electrical functions in the brain. Seizure is a common disorder in childhood as it occurs in 10% of them. Less than one third of seizures that occur in children are due to epilepsy in which the seizures are motivated from inside the brain repeatedly. Epidemiologically, epilepsy is defined as a condition in which 2 or more un-motivated seizures occur with an interval of more than 24 hours (1).
Treatment with antiepileptic agents has a lot of complications such as affecting the function of endocrine glands (e.g. thyroid) and bone marrow healthiness (2).
Many drugs can change plasma levels of T3 and T4. Among these medications,

antiepileptic agents such as Phenobarbital, Phenytoin, Carbamazepine and Sodium Valproate are of importance since if their changes are not identified, they can lead to misinterpretation of thyroid function tests. These drugs are powerful inducers of liver microsomal enzymes which can result in changing the metabolism of thyroid hormones (2).

In various studies, different results have been achieved regarding the effect(s) of antiepileptic medications on thyroid function tests (3-5).Thus, considering the high incidence of seizure in the first years of life and the high usage of antiepileptic agents and also the fact that thyroid gland dysfunction in neonates and children can lead to growth and developmental retardation (1), the current study was designed to evaluate thyroid function tests in children who use antiepileptic medications in an attempt to adentify the drug with the fewest complications.

Materials & Methods

This analytical-observational study was carried out in a cohort fashion without an external control group (self controlled) on 47 children with epilepsy who were referred to the pediatric ward of Shahid Beheshti Hospital, Kashan. They had not received any antiepileptic medications prior to the study. After explaining the stages of the study to the parents, every child who was hospitalized in the pediatric ward with the diagnosis of epilepsy (2 or more un-motivated seizures with an interval of more than 24 hours) was included in the study. Patients with disturbed thyroid function tests in this stage (before study) were excluded the study (2 subjects) and three subjects were excluded from the study because of developing symptoms of hypothyroidism such as constipation, lethargy, loss of appetite and low activity and were therefore referred to an endocrinologist. So, the study was carried out with 42 subjects (all analyses were done on this sample size). Inclusion criteria included new cases of epilepsy, no history of using antiepileptic medications or any other drug that may affect thyroid gland function and no history of endocrine, cardiovascular, neurometabolic or other chronic diseases.

Before starting the treatment with antiepileptic agents, a 5 CC heparinated blood sample was taken by a pediatric ward nurse and sent to laboratory in order for thyroid function tests, including TSH, T3, FT3, T4 and FT4, to be evaluated. All laboratory evaluations were handled by a technician who was blinded to the study through RadioImmunoAssay (RIA). The normal range of T3, T4 and TSH plasma levels were 1.19-1.7ng/ml, 5.5-13µg/dl and less than 5µU/ml, respectively. Tests results of each patient were recorded in an information sheet. After the patients passed the acute phase of seizure, they underwent treatment with antiepileptic agents including Carbamazepine 20mg/kg, Phenobarbital 5mg/kg and Sodium Valproate 25mg/kg (1). Choosing the medicine was with regard to the seizure type. Three and six months after treatment with antiepileptics, thyroid function tests were re-evaluated in the same laboratory and their results were recorded in the information sheets. All subjects were asked if they used other medications that could affect thyroid function tests or if they developed endocrine or other diseases during the study. It should be mentioned that 2 patients who were receiving Sodium Valproate and one patient who was treated with Carbamazepine were excluded from the study because of developing symptoms at the end of the third month and were then referred to an endocrinologist. Patients' information was collected using a holistic questionnaire that was prepared based on the variables of the study. Relevant information was extracted from the information sheets and data analysis was performed via appropriate abundance tables based on study variables. Data was analyzed with Repeated Measurement statistical test (Friedman model) using SPSS#13 software in order to compare the tests results. A statistical lower limit of 0.05 was considered for significance in Friedman test. Significant results were processed with Mann Whitney test with a significance level of 0.017 because of making comparisons for three times. Comparisons were made between plasma levels of hormones at baseline and after 3 and 6 months and also between plasma levels of hormones after 3 months and after 6 months (Tables 1, 2).

Results

Fifteen subjects received Carbamazepine therapy, 15 subjects were treated with Sodium Valproate and 12 subjects underwent Phenobarbital therapy. Mean age of the subjects was 7.62 years (minimum 4 and maximum 13 years old).

The decrease in the plasma level of FT3 was only

significant in the Sodium Valproate group. T4 plasma level decreased significantly in all 3 groups of Carbamazepine, Sodium Valproate and Phenobarbital 3 and 6 months after treatment while FT4 plasma level decreased significantly only in the Carbamazepine group 6 months after treatment. Table 1 shows mean plasma levels of thyroid hormones at baseline and 3 and 6 months after treatment. The results of Mann Whitney test showed that the increase in the plasma level of TSH was only significant in the Sodium Valproate group. Only subjects in the Phenobarbital group showed a significant decrease in T3 plasma level 3 and 6 months after the onset of treatment.

Discussion

As mentioned, various differences in thyroid function tests were seen in patients who received antiepileptic medications. Other studies have reached similar conclusions as Cansu et al. (2006) evaluated 55 children with epilepsy who were treated with Sodium Valproate and Carbamazepine in Turkey. He suggested that in patients on Carbamazepine treatment, plasma levels of FT4, T4, FT3, and T3 decreased significantly ($P<0.05$). Also, in children receiving Sodium Valproate, plasma levels of FT4, T4, FT3, and T3 were within normal range and the same as baseline but TSH plasma level increased significantly 6 months after treatment ($P<0.05$). Subclinical hypothyroidism was seen in patients treated with Sodium Valproate (5).

In the current study, only patients treated with Sodium Valproate experienced a significant increase in the plasma level of TSH. However, patients who were treated with Carbamazepine showed an increase in the plasma level of FT3 and a decrease in the plasma levels of T4 and FT4.

Vainionpaa et al. (2004) compared plasma levels of thyroid hormone between 41 children treated with Carbamazepine and 19 children treated with Sodium Valproate, with 54 healthy volunteers as the control group in Finland. Children treated with Carbamazepine showed a significant decrease in plasma level of T3 and T4 but the level of TSH was normal. Children treated with Sodium Valproate showed an increase in TSH level but the plasma levels of T3 and T4 were normal (6).

Hegedus et al. (1989) compared 28 patients who were treated with Carbamazepine and volunteers in the control group in Spain. Mean plasma level of T3 and T4 decreased in patients (7).

In the mentioned studies as well as the current study, a significant decrease in T4 plasma level was seen in children treated with Carbamazepine but no significant change in T3 plasma level was seen in them.

Mikati et al. compared thyroid gland function between 143 children treated with Sodium Valproate and 35 children as a control group. Subclinical hypothyroidism was recorded in 25.2% of the patients; however, none of children in the control group developed subclinical hypothyroidism ($P<0.001$) (8).

In the current study, subclinical hypothyroidism was also recorded in children treated with Sodium Valproate.

Hirfanoglu et al. (2007) evaluated thyroid gland function between 12 children treated with Carbamazepine and 31 children treated with Sodium Valproate in Turkey. T4 mean plasma level in patients treated with Carbamazepine was significantly lower than the group treated with Sodium Valproate ($P<0.016$). TSH showed no significant difference in either group (9).

Tanaka et al. evaluated 287 children who received antiepileptic medication (26 children treated with Carbamazepine, 63 children treated with Phenobarbital, 66 children treated with Sodium Valproate and 132 children treated with several medications). A Decrease in the mean plasma level of T4 and T3 was recorded in patients treated with Carbamazepine and Phenobarbital but not in patients treated with Sodium Valproate (10).

Similar to the above-mentioned study, in the current study, a decrease in T3 plasma level was seen in patients treated with Phenobarbital as well as a significant decrease in plasma level of T4 in patients treated with Carbamazepine and Phenobarbital.

Regarding the effects of antiepileptics on central nervous system, some studies have examined the hypothesis that antiepileptic agents can decrease plasma levels of hormones, because of their central effects on hypothalamus-pituitary-thyroid axis. Except for some limited studies (5-12) that showed a decrease in the plasma levels of hormones due to the central disturbance induced by such medications, the majority of them (13-14) did not suggest any problems in the hypothalamus-pituitary-thyroid axis.

Another hypothesis is that Carbamazepine increases the metabolism of thyroid hormones through activating the P450 enzymatic system in the liver (6).

As seen previously, there are a variety of changes in thyroid function tests in patients who receive antiepileptic medications and most of them are related to Sodium Valproate. Phenobarbital and Carbamazepine, as mentioned earlier, have fewer effects on thyroid function tests. In our patients who were treated with Sodium Valproate, a significant increase in TSH level and a decrease in T4 and FT3 were obvious and in patients treated with Carbamazepine, a significant decrease in T4 and FT4 were seen. In patients treated with Phenobarbital, T3 and T4 significantly decreased. Unlike many other studies, we also investigated the effect of Phenobarbital on thyroid hormones in epileptic children.

In the end, we suggest that TFT (Thyroid Function Tests) be evaluated in the children who receive antiepileptic therapy.

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Table 1. Laboratory data in epileptic children treated with Carbamazepine, Sodium Valproate AND Phenobarbital

therapeutic regimen / plasma level		Carbamazepine (x ± SD)	Sodium Valproate (x ± SD)	Phenobarbital (x ± SD)
TSH	Before treatment	2.75±1.35	3.74±1.35	3.22±1.40
	3 months after	2.75±1.35	4.85±1.68	3.25±1.41
	6 months after	2.77±1.35	4.48±1.67	3.41±1.36
P-value		0.368	0.0001	0.044
T3	Before treatment	139.28±22.60	143.87±27.48	153.66±21.64
	3 months after	140.07±22.88	162.81±83.77	152.25±21.59
	6 months after	140.07±22.88	162.81±83.77	152.25±21.59
P-value		0.276	0.069	0.001
FT3	Before treatment	354.14±125.20	372±138.61	429.16±150.78
	3 months after	355.92±126.02	370.37±138.88	428.33±150.76
	6 months after	355.92±126.02	370.37±138.88	428.33±150.76
P-value		0.001	0.0001	0.165
T4	Before treatment	9.05±1.55	8.49±1.84	8.02±1.58
	3 months after	5.87±0.87	8.25±1.64	7.86±1.59
	6 months after	5.52±0.8	8.25±1.64	7.86±1.59
P-value		<0.0001	<0.0001	<0.0001
FT4	Before treatment	1.62±0.21	1.56±0.32	1.48±0.32
	3 months after	1.57±0.26	1.46±0.32	1.44±0.28
	6 months after	1.54±0.25	1.46±0.32	1.44±0.28
P-value		0.004	0.007	0.018

(P-value<0.05 is significant)

Table 2. Thyroid hormones plasma level statistical analysis in 3 and 6 months after treating epileptic children, using Mann-Whitney method.

plasma level \ therapeutic regimen		Carbamazepine	Sodium Valproate	Phenobarbital
TSH	Baseline and 3 months	1	0.003	0.473
	Baseline and 6 months	0.194	0.003	0.101
	3 months and 6 months	0.194	0.317	0.068
T3	Baseline and 3 months	0.121	0.141	0.016
	Baseline and 6 months	0.121	0.141	0.016
	3 months and 6 months	1	1	1
FT3	Baseline and 3 months	0.018	0.007	0.078
	Baseline and 6 months	0.018	0.007	0.078
	3 months and 6 months	1	1	1
T4	Baseline and 3 months	0.001	0.011	0.011
	Baseline and 6 months	0.001	0.011	0.011
	3 months and 6 months	0.043	1	1
FT4	Baseline and 3 months	0.039	0.039	0.059
	Baseline and 6 months	0.016	0.039	0.059
	3 months and 6 months	0.102	1	1

(P-value<0.017 is significant)

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