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Neuropsychological impairment and altered thyroid hormone levels in epilepsy

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ABSTRACT

Background. Neuropsychological impairment is a common problem in epilepsy which interferes with the quality of life of patients. Similarly, thyroid hormone levels have been observed to be abnormal in patients with epilepsy on various treatments. This study aimed to ascertain any possible correlation between neuropsychological performance and thyroid hormone levels among epilepsy patients.
Methods. Thyroid hormone levels, indices of neuropsychological performance and social adaptation of 43 epilepsy patients were compared with those of age- and sex-matched healthy control subjects.
Results. Epilepsy patients exhibited significantly ($p<0.001$) lower scores on attention, memory, constructional praxis, finger tapping time, and verbal intelligence quotient (IQ) when compared with controls. Their T3, T4 and Free T3 levels were significantly lower; and TSH and Free T4 levels were significantly higher than that of controls. There was no statistically significant correlation between the indices of neuropsychological performance and thyroid hormone levels.
Conclusion. We did not observe any correlation between neuropsychological impairment and thyroid hormone levels among patients with epilepsy.
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INTRODUCTION

Psychosocial adaptation and quality of life in epilepsy depend, to a large extent, upon neuropsychological performance, especially attention and memory.[1] Recent studies have shown that neuro.psychological performance is influenced by many factors. These include intractability of seizures, impact of coexisting neurological disorders and adverse effects of anti-epileptic drugs (AEDs).[2, 3] Also, cognitive impairments constitute an important aspect of hypothyroidism. Thyroid hormones are essential for the development and maintenance of mental functions in human beings.Seizures can be the presenting symptom of hypothyroidism as well as hyperthyroidism.[4, 5]

As early as 1961, it was observed that diphenyl hydantoin could lower the levels of thyroid hormones.[6] Further reports indicate that phenobarbitone, carbamazepine and sodium valproate also have similar effects on thyroid hormone levels.[7-17]

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clinical relevance of these variations remains to be elucidated. It is generally considered that patients with epilepsy on AEDs are in a euthyroid state (even when the hormone levels in the blood are low) as they do not exhibit any clinical features of hypothyroidism such as weight gain, cold intolerance; and their thyroid stimulating hormone (TSH) levels are not elevated. However, low TSH levels could be spurious as AEDs can alter the pituitary responsiveness to respective hypothalamic stimulating hormones.[18] Hence, there are limitations in interpreting the results of thyroid function tests among patients with epilepsy on AEDs.

Relatively little is known about the relationship between low levels of thyroid hormones and impaired neuropsychological performance or psychosocial maladaptation in epilepsy. The possible link between cognitive decline in epilepsy and changes in thyroid hormone profile in patients with epilepsy needs elucidation. In order to ascertain any possible correlation between neuropsychological performance or psychosocial maladaptation and thyroid function, we studied the thyroid function, neuropsychological performance and psychosocial adaptation in a cohort of patients with epilepsy.

MATERIAL AND METHODS

This study was done at the Epilepsy Clinic, Sree Chitra Tirunal Institute for Medical Sciences and Technology in Thiruvananthapuram, a tertiary referral centre for neurological and cardiac disorders in South India.

Patients and control subjects

Patients older than ten years of age and having recurrent unprovoked seizures for more than two years were included in the study. Exclusion criteria consisted of mental retardation, physical handicap, language disability, other medical or surgical disorders, use of contraceptive pills or medicines other than AEDs, pregnancy and lactation. Patients whose drug dosage had been modified or who had had one seizure in the past month were also excluded. Informed consent was obtained from all the participants.Seizures were classified according to the recommendations of the International League Against Epilepsy.[19] A physical examination with emphasis on the thyroid and the nervous system was performed on all patients. Age- and sex-matched control subjects were selected from the relatives of patients and hospital staff. The exclusion criteria for the patient group were applied to the control group as well.

Thyroid function tests

Thyroid hormone levels were estimated by one of the authors (VP) at the Regional Cancer Centre, Thiruvananthapuram. Triiodothyronine (T3), Tetraiodothyronine (T4), Free T3 (FT3) and Free T4 (FT4) were estimated in the serum by radioimmunoassay (RIA) using kits produced by Diagnostic Products Corporation, .'USA. TSH was assayed by RIA using kits from the Board of Radiation and Isotope Technology, Mumbai.

Neuropsychological tests and indices of social adaptation

The neuropsychological test battery consisted of measures of attention and vigilance (such as reaction time, trail making test and Stroop test), memory [Wechsler memory quotient (WMQ)], verbal intelligence quotient, test for motor agility (finger tapping test) and constructional praxis. Reaction time was measured on a 'computer as the time taken for the patient to press a computer key in response to the appearance of a predetermined symbol on the 'monitor. The finger tapping test counts the maximum number of times a patient can tap a computer key with one finger within three seconds. Psychosocial adaptation of the patients was measured on the Washington psychosocial seizure inventory (WPSI),[20] Mathew's maladjustment inventory (MMI)[21] and score of self-esteem.[22] WPSI estimates social adaptation under eight headings, viz. family background, emotional adjustment, vocational adjustment, financial status, adjustment to seizures, medicine and medical management and overall psychosocial functioning. MMI is a standardized protocol consisting of 25 items that score diverse social maladjustments. The inventory of SE consists of 100 items to quantify self-esteem; The neuropsychological tests and indices of social adaptation were administered by one of the authors in two or three sessions within two days. All the authors were blinded to the results of the other tests.

Statistical analysis

Consecutive cases satisfying the study criteria and consenting for the test were enrolled in this study. The results were compiled in a computer database and were described in terms of mean (standard deviation). For comparing means of groups, Student's' test was used for continuous variables with normal distribution and the Mann-Whitney test was used for ordered variables. Univariate and multivariate regression was carried out using the SPSS PC+ computer software

for ascertaining the association between neuropsychological impairment and thyroid hormone levels. For variables that were not continuous. Spearman's rank correlations were used in place of Pearson's correlation coefficient. In the case of FT3 and FT4, 't' test was done to verify the hypothesis that the epilepsy patient group's mean was not different from that of the control group (provided with the test kits). For all other tests, the comparison was made between the values obtained in epilepsy patients and controls.

RESULTS

Patient characteristics

Forty-three patients (23 men and 20 women) whose mean (SD) age was 28.4 (9.8) years were included in the study. The mean duration of epilepsy was 9.8 (7.1) years. Of these, 43.8% had generalized tonic-clonic seizures, 12.5% had simple partial seizures, 31.8% had complex partial seizures; 12.5% had more than one type of seizure. The frequency of seizures was 5.21 (14.57) persix months. Twenty-nine (68.3%) of them were on monotherapy and the rest were on two drugs; 18.8% were on phenobarbitone, 43.8% on phenytoin, 50% on carbamazepine and 6.3% on sodium valproate. The mean (SD) blood levels of various AEDs in the patients using them were: phenobarbitone 19.07 (9.73) ug/ml, diphenyl hydantoin 10.03 (7.0) ug/ml, carbamazepine 7.9 (1.83) ug/ml sodium valproate 58.0 (6.53) ug/ml.

Thyroid function, neuropsychological performance and social adaptation

None of the patients had any clinical features of hypothyroidism,Their thyroid hormone levels, neuropsychological test results and indices of social adaptation were compared with those of controls (Table I). T4, FT4 and FT3 levels among the epileptics were significantly lower than those in controls. In contrast, the levels of T3 and TSH were significantly higher among the epileptics as compared to controls. However, the TSH levels were well below the cut-off point for hypothyroidism (>5 iu/L) for the laboratory. Epileptics had a significantly lower score on tests of attention, vigilance, memory, constructional praxis and finger tapping. Similarly, their performance was poorer than controls on measures of self-esteem and social adaptation. Correlation coefficients of clinical and neuropsychological characteristics against thyroid function in epileptics are presented in Table II. There was a weak correlation (not statistically significant) between low levels of thyroid hormones and duration of epilepsy and seizure frequency. Hormone abnormality was most pronounced in patients taking diphenyl hydantoin when compared to other drugs.
Multiple regression analyses showed that there was no statistically significant association between thyroid hormone levels and the scores on neuropsychological tests or psychosocial indices.

Table 1. Comparison of mean thyroid hormone levels, neuropsychological test results and indices of psychosocial adaptation among epileptics and normal controls

Item	Epileptics	Controls	p value	95%CI
T4 (pg/dl)	7.4 (4.0)	9.2 (1.7)	0.006	-3.16, -0.58
T3 (ng/dl)	134 (24.6)	122 (40.4)	0.04	0.41, 23.33
FT4 (ng/dl)	0.8 (0.22)	1.4	<0.001	-0.68, -0..53
FT3 (ng/dl)	1.29 (0.81)	2.9	<0.001	-1.88, -1.34
TSH (miu/L)	1.74 (1.13)	1.3 (0.93)	0.031	0.04, 0.84
Wechslermemory quotient	68.35 (14.57)	96.2 (15.66)	<0.001	-33.6, -22.1
Trail making test (seconds)	267.8 (127.9)	137.4 (51.9)	<0.001	97.8, 163.2
Stroop test (seconds)	49.16 (19.9)	29.5 (11.9)	<0.001	12.9, 25.4
Constructional praxis	1.43 (0.73)	2.25 (0.92)	<0.001	na
Verbal intelligence quotient	87.6 (18.1)	111.1 (10.6)	<0.001	-28.7, -18.2
Reactiontime (seconds)	0.782 (0.316)	0.558 (0.195)	<0.001	0.131, 0.317
Finger tapping test	11.53 (3.98)	15.88 (5.07)	<0.001	-6.03, -2.67
Self-esteem	16.49 (3.88)	19.70 (2.83)	<0.001	-4.45, -1.98
MMI	10.4 (5.34)	3.95 (2.64)	<0.001	5.0, 7.9
WPSI	9.04 (6.22)	na	na	na

na not applicable T3 triiodothyronine T4 tetraiodolhyronine TSH thyroid stimulating honnone
FT3 free triiodothyronine FT4 free tetraiodolhyronine MMI Malhew's maladjustment inventory
WPSI Washington psychosocial seizure inventory

Table2. Correlation coefficients of clinical and neuropsycho-logical characteristics against thyroid function in epileptics

Item	T3	T4	TSH	FT3	FT4
Seizure frequency*	0.08	0.05	0.02	0.18	0.12
Duration of epilepsy	0.04	0.23	-0.16	-0.08	-0.33
Serum levels					
Phenobarbitone	0.31	0.31	0.50	0.34	0.17
Diphenyl hydantoin	0.59	0.39	-0.58	0.30	0.22
Sodium valproate	0.39	0.54	-0.74	-0.40	0.92
Carbamazepine	0.23	0.12	-0.04	-0.001	-0.37
Neuropsychological tests					
Trail making test	0.03	0.007	-0.02	-0.04	-0.36
Stroop test	0.01	-0.15	-0.27	0.06	0.11
Reaction time	0.02	-0.03	-0.14	0.18	0.10
WMQ	0.01	0.27	0.08	-0.03	0.02
Constructional praxis*	-0.05	0.27	0.16	-0.01	0.002
WPSI	0.23	-0.15	-0.39	0.35	0.08

T3 triiodothyronine T4 telraiodothyronine TSH thyroid stimulating hormone FT3 free triiodothyronine FT4 free tctraiodoihyroninc
* Spearman's rank correlation coefficient WMQ Wcchsler memory quotient
WPSI Washington psychosocial seizure inventory

DISCUSSION

In this study, patients with epilepsy exhibited significantly lower levels of T4, FT4, and FT3 and significantly higher levels of T3 and TSH compared to controls. Their performance on neuropsychological tests and indices of social adaptation were also significantly poorer than those of controls. The tests for attention, memory and other cognitive functions showed significant impairment among the epileptics. However, there was no correlation between neuropsychological impairment and thyroid hormone levels in the blood. Similarly, there was no correlation between thyroid hormone levels and measures of psychosocial adaptation. Earlier studies have shown that serum levels of thyroid hormones were lower among epilepsy patients on carbamazepine or diphenyl hydantoin and to a lesser extent among patients on phenobarbitone and valproic acid.[10,11,23-28] Different mechanisms have been proposed to explain these variations. Diphenyl hydantoin is known to displace T4 from thyroid binding globulin (TBG) and thereby reduce T4 levels in the blood.[15] AEDs can increase the peripheral catabolism of T4 to T3 and, to a lesser extent, reverse T3 (rT3) by enzyme induction.[23,29,30] This could be one of the reasons for the higher levels of T3 observed among the epileptics in this study. A third mechanism is reduced production ofT4 by the thyroid gland.[31] A majority of earlier studies have also argued that patients on AEDs are apparently euthyroid since their TSH levels remain within the normal range.

This apparent paradox was attributed to a new steady state wherein low levels of T4, FT4 and FT3 do not produce any clinical impairment. This hypothesis is supported by the observation that basal TSH levels as well as TRH-induced TSH levels were normal in epilepsy.[11,23,24] However, other workers have demonstrated a dysfunction of the hypothalamo-pituitary axis as the pituitary response to TRH was blunted in their patients on AEDs.[23] The serotoninergic effects of carbamazepine were implicated to suppress the TSH response to TRH.[32]

How far does the TSH level indicate thyroid function when there is a possibility of impairment of the hypothalamo-pituitary axis in epilepsy patients on AEDs? Recently, it had been shown that patients with epilepsy on carbamazepine had subclinical impairment ofdiastolic function of the myocardium." This change was attributed to low levels of thyroid hormones in these patients even

though they had normal TSH levels and no overt changes due to hypothyroidism. In contrast, we did not observe any correlation between low thyroid hormone levels and cognitive functions of patients with epilepsy. Surks and DeFesi have demonstrated that the FT4 levels remained unchanged in such patients when estimated by ultrafiltration assay, while it was significantly reduced when measured by commercial kits using 1:5 dilution.[34] They suggest that the apparent drop in the blood levels of thyroid hormones in patients with epilepsy on carbamazepine orphenytoin could be due to deficiencies in the techniques of estimation. This hypothesis seems to be supported by our observation that despite low levels of total and free thyroid hormones, TSH levels are not proportionately elevated.

It appears that neuropsychological impairment and social maladaptation among epileptics are independent of the thyroid hormone levels. However, the kinetics of FT3 and FT4 and the differential influence of FT3 *v.* FT4 on cognitive functions needs further elaboration. Thyroid function during active epilepsy needs to be compared with that during remission and off AEDs.

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