Subclinical Hypothyroidism and Dyslipidemia in Upper Egyptian Epileptic Children on Carbamazepine Therapy

Hosny M.A. ElMasry[1], Amira M. M. Hamed[(1)], Mostafa Abd Elazeem H[(1),] Hashem A. Hassan[(2)] and Mohammad M. Abolfotouh[(3)]

Department of Pediatrics [1], neuropsychiatry and Medical Biochemistry[(3)], Faculty of Medicine- Al-Azhar University - Assiut - Egypt

Abstract

Background: long term antiepileptic drug therapy can influence thyroid functions and lipid profile. **Objectives:** to evaluate epileptic children receiving carbamazepine for serum thyroid hormones (total and free T_3, T_4 and TSH) and lipid profile [total cholesterol (TC), Triglycerides (TGs), high density lipoprotein (HDL) and low density lipoprotein (LDL)]. **Patients and methods:** 30 epileptic children on carbamazepine therapy and 15 apparently healthy children as controls aged 2-15 years. Patient group was then subdivided into two subgroups according to the duration of treatment. All patients and controls were subjected assessment of serum thyroid hormones and lipid profile. **Results:** The mean serum levels of total and free T_4 in patient group was significantly lower than that of control group ($p=0.01$ & 0.004 respectively), while the mean serum levels of total and free T_3 and TSH were not significantly different ($p>0.05$). The mean serum levels of cholesterol, triglycerides and LDL in patients with prolonged duration of therapy was significantly higher than those patients with shorter duration of therapy. Significant negative correlations were found between serum levels of thyroid hormone and lipid profile while significant positive correlations were found between duration of carbamazepine therapy and serum lipid profile. **Conclusions:**

subclinical hypothyroidism and hyperlipidemia were observed in epileptic children on carbamazepine therapy.

Keywords: epileptic children, carbamazepine, lipid profile and thyroid function.

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Introduction

Epilepsy is a common chronic medical problem affecting 0.5– 1.5% of the world population, it is either of unknown etiology (idiopathic epilepsy) or due to congenital or acquired brain lesions (symptomatic or secondary epilepsy) (Weissel; 2003).

Carbamazepine (CBZ) is considered one of the first drugs in treatment of partial and secondarily generalized seizures *(*Loiseau et al; 2002 and Alberto *et al; 2009)* .Carbamazepine is a commonly used antiepileptic drug, it is metabolized in the liver and induces activation of hepatic microsomal enzymes leading to alterations in the metabolism of cholesterol and other lipids *(Garcia and Moodie, 2004).*

CBZ therapy can decrease the serum thyroid hormone levels, but generally serum thyrotropin-releasing hormone (TSH) concentrations remain normal except in a small percentage of patients who show increased TSH levels (*Verrotti et al., 2001&* Alberto *et al; 2009* and Yılmaz *et al; 2013*).

Long term antiepileptic drug therapy have a significant influence on TC, HDL, LDL and TGs *(*Mintzer et al; 2009 and Rai *et al; 2010).* Hyperlipidemia is one of the major risk factors for atherosclerosis, the first sign of which can be detected during childhood, antiepileptic drugs may alter the serum lipid profile of children in such a way that could potentially facilitate the development of atherosclerosis *(Gorcia and Moodie, 2004).*

Aim of the Work: This study aimed to assess serum thyroid hormones (total and free T_3, T_4 and TSH) and lipid profile (TC, TGs, HDL and LDL,) in epileptic children receiving carbamazepine.

Patient and methods: This study was conducted at Al Azhar Assiut university hospital – Upper Egypt on 30 epileptic children (patient group, 14 males & 16 females) and 15 apparently healthy (control group, 7 males & 8 females,) children aged 2-15 years. Patient group was then subdivided into two subgroups according to the duration of treatment.

- **Group A:** (18 children with a mean ± SD duration of therapy 1.7±0.61years) &
- **Group B:** (12 children with a mean ± SD duration of therapy 2.9±0.56 years).

All patients and controls were subjected to thorough history taking, complete clinical examination and the following investigations: CBC, liver function tests, serum thyroid hormones (Total and free T_3, T_4 and TSH), serum lipid profile (TC, TGs, HDL and LDL) in addition to assessment of serum level of carbamazepine for patient group. Children younger than 2 years or older than 15 years of age, those having chronic liver, renal or heart disease, obesity, diabetes mellitus, chromosomal disorders, children with family history of hyperlipidemia or atherosclerosis, malnourished and stunted children, those suffering from hypo or hyperthyroidism, and those receiving antiepileptic drugs other than carbamazepine and children on poly-drug therapy were excluded from this

study, in addition , patients with serum levels of carbamazepine beyond the normal therapeutic range (8–12 µg/ml) were also excluded from this study.

Blood was drawn from patients and controls by venipuncture after an overnight fasting, serum was separated by centrifugation for assessment of serum thyroid hormones, lipid profile and carbamazepine serum levels.

Assessment of thyroid hormones:

Total T_3 & T_4: The micro plate enzyme immunoassay method was used, Reference range: 44–108 nmol/L for Total T_4 *and* 0.5–2.2 ng/mL for Total T_3 *(Chopra et al., 1981).*

Free T_3 & T_4: I^{125} labeled T_4 or I^{125} labeled T_3 analog competes for a fixed time with free T_4 or free T_3 respectively in the patient sample for sites on T_4 or T_3 specific antibody immobilized to the wall of a polypropylene tube, the tub e is then decanted to isolate the antibody–bound fraction and counted in a gamma counter, the counts being inversely related to the concentration of free T4 or free T3 in the sample. Reference range: 0.8–2.2 ng/dL for free T4 *(Surks and Defesi, 1996)* & 2.3–6.6 ng/dL for free T3 *(Isojarvi et al., 1990).*

TSH: Coat–A–count TSH IRMA is a solid phase immunoradiometric assay based on monoclonal and polyclonal anti–TSH antibodies. Reference range: 0.7–6.4 miu/L *(Spencer et al., 1995).*

Assessment of serum lipid profile:

TC: it is determined after enzymatic hydrolysis and oxidation was done using enzymatic colorimetric test, the colorimetric indicator is a chinoneimine which is generated from 4 amino antipyrine and phenol by hydrogen peroxide under the catalytic

action of peroxidase. Reference range was variable according to age Suspected > 200 mg/dL – Elevated > 260 mg/dL *(Chiarelli et al., 1995).*

TGs: enzymatic hydrolysis of triglycerides with subsequent determination of the liberated glycerol by colorimetry. Reference range: variable according to age. Suspected > 150 mg/dL - elevated > 200 mg/dL *(Havel et al., 1997).*

HDL: chylomicrons, VLDL and LDL are precipitated by adding phosphotungistic acid and magnesium ions to the sample. Centrifugation leaves only HDL in the supernatant and their cholesterol content is determined enzymatically. Reference range: variable according to age. Suspected > 80 mg/dL. Elevated > 120 mg/dL *(Chiarelli et al., 1995).*

LDL: it is calculated from the following equation LDL = TC-(HDL + 1/5 TGs). Reference range: variable according to age. Suspected > 170 mg/dL elevated > 200 mg/dL *(Havel et al., 1997).*

Statistical Method: The data were analyzed using SPSS 8.0, Chicago, IL, USA. Statistical significance was considered to be achieved when P value was less than 0.05

Results

The results of the different variables in the studied patients (n=30) and controls (n=15) are shown in tables (1 -3) and figures (1-3). In our study we found that, 24 cases (80%) have generalized tonic-clonic convulsions, while 3 cases (10%) have generalized tonic convulsions and 3 cases (10%) have partial seizures.

Table (1): Mean ± SD serum levels of thyroid hormones in patient and control groups

Serum thyroid hormones	Control group (n=15)	Patient group (n=30)	P value
Total T_4 (nmol/L)	96.6 ± 7.1	70.2 ± 6.7	0.01**
Free T_4 (ng/dL)	1.8 ± 0.3	1.4 ± 0.4	0.004**
Total T_3 (ng/mL)	1.5 ± 0.7	1.3 ± 0.9	0.3
Free T_3 (ng/dL)	5.5 ± 0.7	5.2 ± 0.6	0.2
TSH (miu/L)	2.5 ± 1.0	2.7 ± 1.4	0.2

**: P value is highly significant ($p < 0.005$)

Table (2): Mean ± SD levels of serum lipid profile in patient and control groups

Serum lipids (mg/dL)	Control group (n=15)	Patient group (n=30)	P value
Total cholesterol	126.5 ± 33.3	150.7 ± 24.5	0.01**
Triglycerides	84.3 ± 37.0	110.0 ± 34.1	0.03*
High density lipoprotein	37.2 ± 13.5	40.9 ± 13.6	0.4
Low density lipoprotein	72.4 ± 13.6	92.5 ± 25.0	0.02*

*: P value is significant ($p < 0.05$) **: P value is highly significant ($p < 0.005$)

N.B: The mean levels of Serum lipid profile and Serum thyroid hormones showed no statistically significant differences between male and female in patient and control groups.

Table (3): Mean ± SD serum levels of lipid profile and thyroid hormones according to duration of therapy for patient group

Groups Duration of therapy (M±SD)	Group A (n = 18) (1.7±0.61)	Group B (n = 12) (2.9±0.56)	P value
Serum thyroid hormones			
Total T_4 (nmol/L)	76.3 ± 8.2	61.6 ± 7.3	0.04*
Free T_4 (ng/dL)	1.5 ± 0.6	1.3 ± 0.2	0.3*
Total T_3 (ng/mL)	1.4 ± 0.7	1.3 ± 0.6	0.7
Free T_3 (ng/dL)	5.1 ± 0.2	5.0 ± 0.9	0.4
TSH (miu/L)	2.6 ± 1.3	2.7 ± 1.0	0.3
Serum lipids (mg/dL)			
Total cholesterol	143.5 ± 16.5	158.2 ± 17.1	0.04*
Triglycerides.	108.7 ± 25.6	125.3 ± 22.0	0.02*
LDL	83.8 ± 21.6	96.7 ± 18.0	0.05*
HDL	41.4 ± 11.8	40.0 ± 13.5	0.4

*: p value is significant ($p < 0.05$)

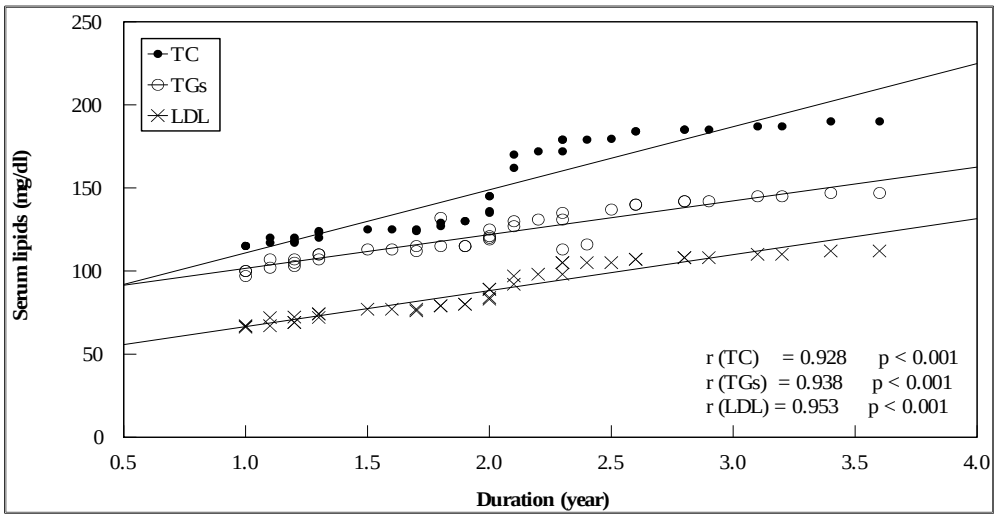

Figure (1): Correlation between serum total T4 and serum lipids in patient group.

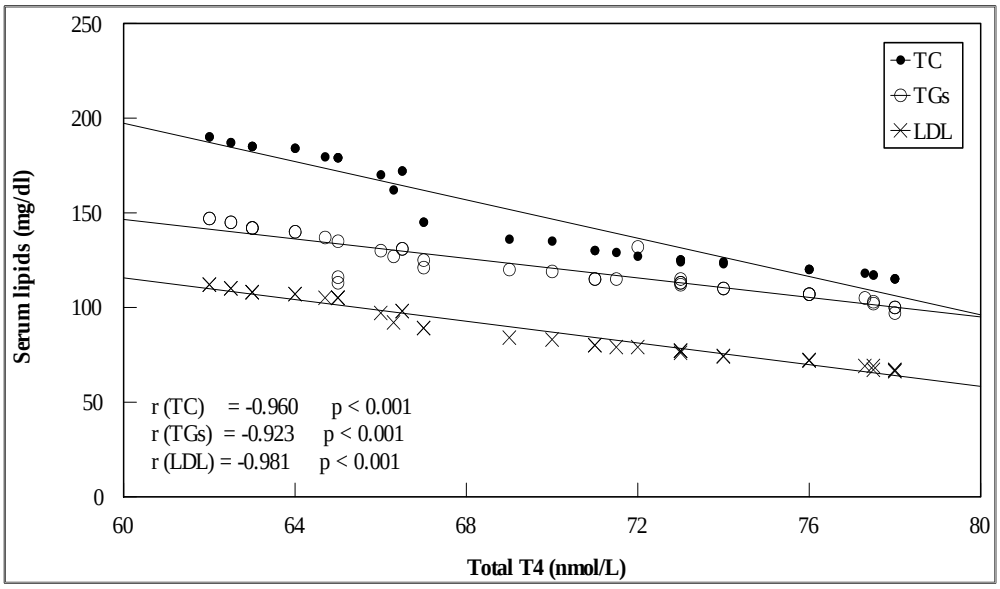

Figure (2): Correlation between duration of therapy and serum lipids in patient group.

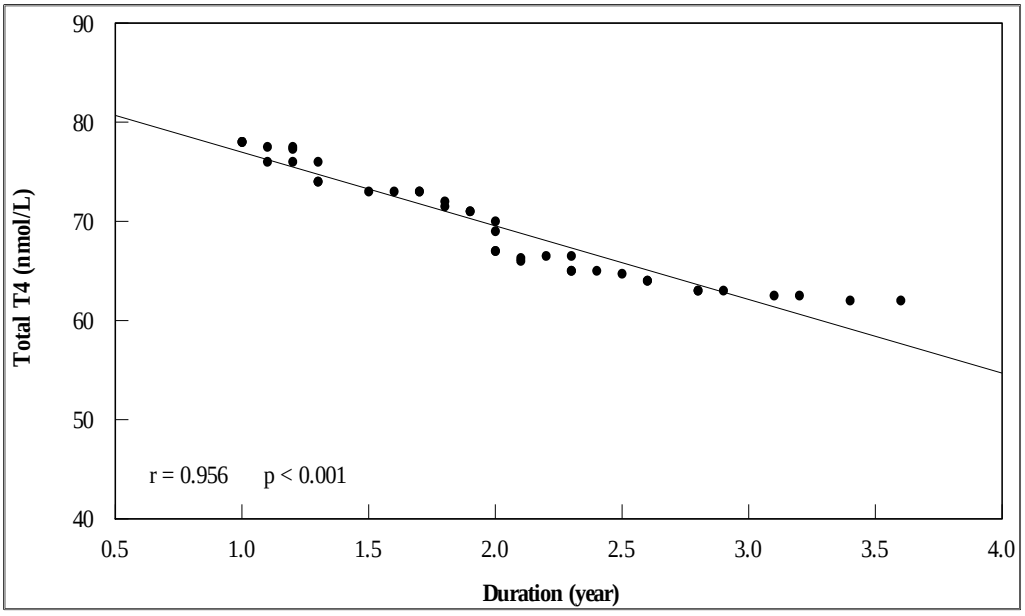

Figure (3): Correlation between duration of therapy and serum total T4 in patient group.

Discussion

In our study, generalized tonic-clonic convulsions were the predominant type of convulsions where it occurred in 80% of epileptic children. This result was in agreement with *Yilmaz et al.; 2001*.

In the current study the mean serum levels of total and free T_4 in patient group was significantly lower than that of control group (p=0.01 & 0.004 respectively), while the mean serum levels of total and free T_3 and TSH were not significantly different from those of the control group (p>0.05) (table 1). These results are in agreement with those reported by Yılmaz *et al; 2013*. Previous studies also reported similar results; *(Verroti et al., 2001; Isojarvi et al; 2001 and Caksen et al., 2003 Vainionpaa et al.; 2004).* However in contrary to our results, a study done by *Surks and Defesi; 1996* reported normal serum *levels of total and free T4 in epileptic children treated with carbamazepine. Despite the* low mean serum levels of total and free T_4 in our study, all patients were clinically euthyroid. Similar to our results *Spacilova et al., 2003 and Weissel, 2003* statd that Subclinical hypothyroidism was relatively a common condition with incidence of 3-7% in the general population. Therefore they suggested that these frequency rates might be increased among patients with epilepsy.

The decreased serum T_4 in patients receiving carbamazepine therapy could be attributed to the induction of hepatic P-450 enzyme system and the consequent increase in the metabolism of thyroid hormones *(*Alberto *et al; 2009* and Aggarwal et al, 2009*).*

A drug induced reduction in the protein binding of thyroid hormone caused by carbamazepine may be also responsible, but it is of minor role *(*Aggarwal *et al; 2011).* Hypothalamic interference of regulation of thyroid hormone production, caused by these drugs, seems possible *(Isojarvi et al., 2001 and Vainionpaa et al., 2004).*

In our study, we found that the levels of total and free T_4 in group B, with mean ± SD duration of therapy of 2.9 ± 0.56 years, was significantly lower than those in group A, with mean ± SD duration of therapy of 1.7 ± 0.61 years). The levels of total and free T_3 and TSH were not significantly different between the two groups.

Regarding serum lipid profile in epileptic children receiving carbamazepine our study showed that the mean serum levels of total cholesterol, triglycerides and low density lipoprotein in patient group was significantly higher than control group (p=0.01, 0.03 &0.02 respectively), while the mean serum levels of high density lipoprotein was not significantly different from that in the control group (p > 0.05) (table 2). These findings were in agreement with *Eiris et al., 2000; Bramswig et al., 2003 ; Nikolaos et al., 2004, Mahmoudian et al., 2005,* Aggarwal et al, 2009, Mintzer et al; 2009 and Rai *et al; 2010).* In contrast to our results *Deda et al.; 2003,* reported normal serum cholesterol during carbamazepine therapy in epileptic children.

As regard to the effect of duration of carmazepine therapy on lipid profile in our study, we found that the mean serum levels of cholesterol, triglycerides and LDL in group B was significantly higher than those in group A. while the serum level of HDL is not significantly different between the two groups. These results are in agreement with *Mahmoudian et al; 2005.* These results could be explained on the basis of hepatic enzyme inducing effect of antiepileptic drugs including carbamazepine which is metabolized mainly in the hepatic P-450 system. These enzymes also catalyze the biotransformation of cholesterol and other lipids. Thus, chronic use of carbamazepine may compete with lipids in the utilization of these enzymes, leading to decreased biotransformation of these lipids and increase of their levels in the blood *(Mahmoudian et al., 2005).* This supports our results where significant positive correlations were found between duration of carbamazepine therapy and serum lipid profile (figure 3).

In our study, we observed that 15 (50%) of patients have both thyroid dysfunction (decreased total and free T_4) and abnormal lipid profile (high TC, TGs and LDL). These findings support the presence of a significant negative correlation between serum levels of thyroid hormone and lipid profile (figure 1). Therefore, we suggest that hepatic enzyme induction may not be the main or the only cause for elevated serum lipids in our patients. Elevated serum lipids may be caused by either the effect of carbamazepine on thyroid hormones or may be a still unknown mechanism. However *Deda et al., 2003* have reported normal serum lipids in epileptic patients during carbamazepine therapy.

Thyroid hormones are well known to be involved in the regulation of lipids and lipoproteins metabolism, inducing significant changes in their sizes and concentrations *(Bramswig et al., 2002 and Huesca et al., 2002).* Many studies suggested that carbamazepine not affect cholesterol and other lipids directly nor by decreased catabolism which occur secondary to hepatic enzyme induction, but it changes the conversion cascade of intermediate density lipoprotein (IDL) by most likely indirect effect through a decrease in thyroid hormones *(Isojarvi et al., 2001; Verrotti et al., 2001 and Bramswig et al., 2002).* Some studies demonstrated that a significant reduction in both total cholesterol and LDL concentrations has been reported after administration of thyroxin in a group of hypercholesterolemic patients with basal TSH levels in the upper range of normal values *(Deschampheleire et al., 1999 and Canturk et al., 2003).* In general, a higher prevalence of subclinical hypothyroidism in a population with hypercholesterolemia was determined when compared to a population with normal cholesterol levels *(Spacilova et al., 2003).* Previous studies have demonstrated that, there is an interaction between individual lipids in patients with epilepsy during anticonvulsant treatment. Epileptic patients with elevated TGs or a combination of elevated TGs and LDL have been found to have lower plasma HDL level than

normolipidemic patients with epilepsy *(Luoma et al., 1990).* Some experimental studies demonstrated that in rats and pigs, HDL cholesterol ester can be transformed to LDL despite the absence of plasma cholesterol ester transfer protein and hepatic lipase activity, both are important proteins that modulate the metabolism of HDL. This study also reported that the magnitude of conversion of HDL to LDL is related to the level of cholesterol ester, as induced by the amount of fat in the diet. Hence, high amount of fat in the diet increases the conversion of HDL to LDL *(Geelen et al., 2001).*

In conclusions, lipid abnormalities encountered in patients with epilepsy during carbamazepine therapy cannot be explained by hepatic enzyme induction as the only or the main cause but subclinical hypothyroidism caused by carbamazepine, appear to have an important role in the pathogenesis of elevated serum lipids in these patients. Therefore monitoring of serum lipids and thyroid hormones in epileptic patients on prolonged carbamazepine therapy should be recommended.

References

1. Aggarwal A, Rastogi N, Mittal H, Chillar N, Patil R. Thyroid hormone levels in children receiving carbamazepine or valproate. Pediatr Neurol. 2011 Sep; 45(3):159-62. doi: 10.1016/j.pediatrneurol. 2011.04.005.

2. Aggarwal A, Singh V, Batra S, Faridi MM, Sharma S. Effect of carbamazepine therapy on serum lipids in children with partial epilepsy. Pediatr Neurol. 2009 Feb; 40(2):94-7. doi: 10.1016/j.pediatrneurol. 2009,10.003.

3. Alberto Verrotti, Melissa Laus, Alessandra Scardapane, Emilio Franzoni1 and Francesco Chiarelli Thyroid hormones in children with epilepsy during long-term administration of carbamazepine and valproate. European Journal of Endocrinology (2009) 160 81–86

4. Bramswig, S., Kerksick, A., Sudhop, T., Luers, C., von Vergma, K., Berthold, and H.K. Carbamazepine increases atherogenic lipoproteins: mechanism of action in male adults. Heart Circ Physiol. 2002, 282(2): 704-716.

5. Bramswig, S., Sudhop, T., Luers, C. et al. Lipoprotein (a) concentration increases during treatment with carbamazepine. Epilepsia. 2003, 44(3): 457-460.

6. Caksen, H., Dulger, H., Cesur, G. et al. Evaluation of thyroid and parathyroid functions in children receiving long-term carbamazepine therapy. Int J Neurosci. 2003,113(9): 1213-1217.

7. Canturk, Z., Cetinarslan, B., Tarkun, I., Canturk, N.Z., Ozden, M. Lipid profile and lipoprotein (a) as a risk factor for cardiovascular disease in women with subclinical hypothyroidism. EndocrRes. 2003, 29(3): 307-316.

8. Chiarelli F, Verotti A, Morgese G. Influence of puberty on lipids and lipoprotein profile in children with type I diabetes mellirus. Acta Diabetol. 1995, (32): 102.

9. Chopra IJ, Solomon DH, Ho RS. Radioimmunoassay of thyroxin and Triiodothyronine. J clinical Endocrinol.1981, (33): 865.

10. Deschampheleire, M., Luyckx, F.H., Scheen, A.J. Thyroid disorders and dyslipidemias. Rev Med Liegs. 1999, 54(9):746-750.

11. Eiris, J., Novo, R.M., Del-Rio, M. et al. The effects on lipid and lipoprotein serum levels of long-term carbamazepine, valproic acid and Phenobarbital therapy in children with epilepsy. Epilepsy Res. 2000, 41(1): 1-7.

12. Garcia, K.E., Moodie, D.S. Plasma HDL cholesterol in epileptic children treated with various anticonvulsants pediatrics.2004, (4): 19-25.

13. Geelen, S.N., Lemmens, A.G., Terpstra, A.H., Wensing, T., Beynen, A.C. High density lipoprotein cholesteryl ester metabolism in the pony, an animal species without plasma cholesteryl ester transfer protein activity: transfer of high density lipoprotein cholesteryl esters to lower density lipoproteins and the effect of the amount of fat in the diet. Comp Biochem Physiol B Biochem Mol Biol. 2001, 130(2): 145-154.

14. Havel RJ, Eder HA, Bradgon JH. The distribution and chemical composition of ultra- centrifugally separated lipids and lipoproteins in normal serum. J Clin Invest. 1997, (34): 1345.

15. Huesca-Gomez, C., Franco, M., Luc, G., Montano, L.F., Masso, F., Posadas-Romero, C., Perez-Mendez, O.. Chronic hypothyroidism induces abnormal structure of high-density lipoproteins and impaired kinetics of apoplipoprotein A-I in the rat. Metabolism. 2002, 51(4): 443-450.

16. Isojarvi, J.I.T., Pakarinen, A.I., Ylipalosaari, P.J. et al. Serum hormones in male epileptic patients receiving anticovulsant medication. Arch Neurol. 1990, (47): 670-676.

17. Isojarvi, J.I.T., Turkka, J., Pakarinen, A.J. et al.Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. Epilepsia. 2001, (42): 930-

934.

18. Loiseau P. Carbamazepine: clinical efficacy and use in epilepsy. In Antiepileptic Drugs, edd 5, ch 23, pp 262–272. Eds RH Levy, RH Mattsson, BS Meldrum & E Perucca, Philadelphia: Lippincott Williams & Wilkins, 2002.

19. Luoma, P.V., Myllyla, V.V., Sotaniemi, E.A., Lehtinen, I.A., Hokkanen, E.J. Plasma high-density lipoprotein cholesterol in patients with epilepsy treated with various anticonvulsants. Eur Neurol. 1990, 19(1): 67-72.

20. Mahmoudian, T., Iranpour, R., Messri, N. Serum lipid levels during carbamazepine therapy in epileptic children. Epilepsy and Behaviour. 2005, (6): 257-259.

21. Mintzer S, Skidmore CT, Abidin CJ, Morales MC, Chervoneva I, Capuzzi DM, Sperling MR. Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. Ann Neurol. 2009 Apr; 65(4):448-56.

22. Nikolaos, T., Stylianos, G., Irini, P. et al. The effect of long term antiepileptic treatment on serum cholesterol (Tc, HDLc, LDLc) and triglyceride levels in adult epileptic patients on mono-therapy. Med-Sci-Monit, 200410(4): 50-52.

23. Rai Yogesh Kumar, Misra Harsh and Misra Asha. Effect of anticonvulsant drugs on lipid profile in epileptic patients. Indian Journal of Public Health Research & Development. 2010, Volume : 1, Issue : 1, 46-50.

24. Spacilova, J., Limanova, Z., Aschermann, M. Subclinical hypothyroidism with emphasis on the cardiovascular system. Endocrinol Res, 2003, 142(11): 643-647.

25. Spencer, C.A., Young D.S., Pestaner, L.C. Functional sensitivity of immunometric Assays of thyrotropin (TSH) and impact on reliability of measurement of subnormal concentrations. Clinical Chemistry. 1995 (41): 367.

26. Surks, M.I., DeFesi, C.R. Normal serum free thyroid hormone concentrations in patients treated with phenytoin or carbamazepine. JAMA, 1996, (275): 1495-1498.

27. Vainionpaa, K.L., Mikkonen, K., Johanna, R. et al. Thyroid function in girls with epilepsy with carbamazepine, oxcarbazepine or valproate monotherapy and after withdrawal of medication. Epilepsia. 2004, 45(3): 197-203.

28. Verrotti, A., Basciani, F., Morresi, S. et al. Thyroid hormones in epileptic children receiving carbamazepine and valproic acid. Pediatr Neurol. 2001, (25): 43-46.

29. Weissel, M. Possible consequences of subclinical hypothyroidism. Acta Med Austriaca. 2003, 30(1): 93-97.

30. Yılmaz U, Yılmaz TS, Akıncı G, Korkmaz HA, Tekgül H. The effect of antiepileptic drugs on thyroid function in children. Seizure. 2013 Sep 16. pii: S1059-1311(13)00253-7. doi: 10.1016/j.seizure.2013.09.006.

31. Yilmaz, E., Dosan, Y., Gurgoze, M.K. et al. Serum lipid changes during anticonvulsive treatment in children with epilepsy. Acta Neurol Belg, 2001, 101(4): 217-220.