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The effects of valproate and topiramate use on serum insulin, leptin, neuropeptide Y and ghrelin levels in epileptic children

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ABSTRACT

Purpose: Although some drugs used in the treatment of epilepsy are known to affect body weight, the hormonal factors responsible have not been sufficiently described. The purpose of this study was to compare insulin, leptin, neuropeptide Y and ghrelin levels in children with epilepsy receiving monotherapy with topiramate (TPM) and valproic acid (VPA), the drugs whose effects on body weight have been most discussed, with those of a control group.

Method: 48 patients (25 VPA, 23 TPM) aged between 6 and 15.5 years, presenting to the Karadeniz Technical University Medical Faculty Pediatric Neurology Clinic, diagnosed with idiopathic epilepsy or location-related idiopathic epilepsy, and receiving VPA or TPM monotherapy for at least 6 months were included in the study. Twenty-five healthy subjects with similar demographic characteristics were enrolled as the control group. Blood samples were collected from the patient and control groups after fasting for at least 10–12 h and again 1 and 2 h postprandially. Body mass index (BMI) values were calculated for all cases. VPA levels, glucose, insulin, leptin, neuropeptide Y and ghrelin were investigated in all three separate blood samples.

Results: Age, height, weight and BMI were similar between the patient and control groups. Significant weight gain was observed throughout treatment in the VPA group compared to the TPM group. High fasting and postprandial insulin levels were observed in the VPA group. VPA group leptin and neuropeptide Y (NPY) levels were also higher than in the TPM and control groups. No significant difference was determined in ghrelin levels in the patient groups compared to the controls.

Conclusion: Low blood sugar not being observed, even though insulin levels are high, after fasting and in the postprandial period in epileptic children receiving VPA is indicative of insulin resistance. The elevation in leptin and neuropeptide Y levels observed in the VPA group also suggest this.

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1. Introduction

Some antiepileptic drugs (AEDs) increase body weight, while others are known to lower it [1]. Various mechanisms associated with hormonal effects responsible for this variation have been proposed, but the underlying cause is still unknown. AEDs may stimulate insulin production. Alternatively, carnitine deficiency directly caused by the drug may cause a decrease in glucose levels by lowering fatty acid metabolism. One such mechanism may be that low glucose levels stimulate food consumption via the hypothalamus. Another mechanism may be the appetite-enhancing effect of GABA-mediated neurotransmission. Other less commonly implicated mechanisms include appetite enhancement through an antidiuretic hormone-like effect and norepinephrine or serotonin-mediated effects [2,3].

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The AED whose effect on body weight has been most studied is VPA. The hypotheses proposed to account for the effect of VPA use on weight gain include dysregulation of the hypothalamic system, its effect on adipokine levels, hyperinsulinemia, insulin resistance and genetic susceptibility. Expression of leptin and the adipokine genes that encode neuropeptides such as resistin and fasting-induced adipose factor and leptin, which are involved in the development of insulin resistance and obesity, also increase with VPA therapy [4].

Leptin regulates body weight through the mediation of NPY. Several clinical studies have shown an increase in leptin levels in the presence of weight gain in children receiving VPA therapy [4]. Ghrelin is a polypeptide hormone that can be isolated from the stomach, hypothalamus and other tissues [1]. Ghrelin regulates the release of leptin and insulin. It increases appetite and food intake through its effect on the hypothalamus and also causes weight gain by stimulating hyperinsulinemia [4–6]. The increase in insulin and leptin levels in patients with epilepsy is particularly correlated with the weight increase seen in VPA therapy. Ghrelin levels, however, are generally reported to decrease in epileptic patients.

In this study, we compared the effects of VPA, which is thought to cause weight gain, and TPM, known to lead to weight loss, on various hormones implicated in insulin resistance and weight gain. Our purpose was thus to achieve a better understanding of the mechanisms involved in the side-effects on weight gain caused by these AEDs, whose use starts in childhood and persists for an extended period.

In addition to blood glucose and accompanying insulin values in patient groups receiving VPA and topiramate TPM therapy, this study also investigated levels of the hormones leptin, ghrelin and NPY, which also affect appetite and weight gain. Greater weight gain was observed throughout treatment in the patient group receiving VPA compared to the TPM group. Elevated insulin resistance, NPY and leptin values were also observed in the VPA group.

2. Materials and methods

The study was performed with 48 patients presenting to the Karadeniz Technical University Medical Faculty Pediatric Neurology Clinic and diagnosed with idiopathic generalized or localization-related idiopathic epilepsy based on ILAE-1989, and with a control group of 25 healthy children. Consent was obtained from families agreeing to take part and approval was granted by the Karadeniz Technical University ethical committee. The study was supported by the Karadeniz Technical University Medical Faculty Scientific Research Projects Coordination Unit. Forty-eight patients aged between 6 and 15.5 years, presenting to the Pediatric Neurology Clinic with at least two afebrile episodes, diagnosed with idiopathic generalized or localization-related idiopathic epilepsy based on ILAE-1989 and receiving VPA or TPM monotherapy for at least 6 months were included in the study. Twenty-five of these patients were receiving VPA and 23 were receiving TPM monotherapy.

Before studying, patients were evaluated for endocrinological disorders. Patients with any endocrine disorder were not included in the study. Patients with epilepsy who were suspected of having a metabolic disease were excluded. In addition, genetic and neuro-metabolic disease, which is a dysmorphic facial appearance, was not included in this study. The Patients were selected from among patients were idiopathic epilepsy had no another chronic disease and medication use.

Detailed histories were taken from patients before the study commenced. Conditions for inclusion included complete physical and neurological examination and complete blood count, routine biochemistry tests including liver function tests and full performance of tests such as EEG and MRI routinely used in the monitoring of epilepsy.

The control group was selected from children presenting to the healthy child clinic, in the same age range as the patients, with no chronic disease and with no history of chronic drug use that might affect weight gain (such as steroids).

Serum blood specimens were collected from subjects in the patient and control groups between 08.00 and 09.00 a.m. after at least 10–12 h overnight fasting. Subjects were given a 385–425 calorie breakfast. Blood samples were collected again 1 and 2 h after breakfast. In addition, all subjects were weighed using standard scales and were measured after removing their shoes. Body mass index (BMI) was calculated using the formula weight (kg)/height (m^2). VPA, glucose, insulin, leptin, NPY and ghrelin levels were measured in all three separate blood samples.

Glucose and insulin levels were measured using the chemiluminescent immunoassay method on fully automatic devices (Immulite 2000) and commercial kits at our hospital's Central Biochemistry Laboratory. Leptin levels were assayed using Assaypro and ghrelin and NPY levels using RayBiotech commercial ELISA kits.

Statistical analysis was performed on SPSS 15.0 for Windows software. Descriptive statistics (mean, standard deviation, median) were given for numerical variables. The Kruskal Wallis test was used for numerical comparisons for independent groups without normal distribution and evaluate the significant results by Mann-Whitney *U* test, and used those as a median value with interquartile range (IQR- 25–75%). Friedman's two way analysis was done for repeated measurment. $p < 0.05$ was regarded as statistically significant.

3. Results

The results from 73 cases, including 23 patients (31.5%) using TPM, 25 (34.2%) using VPA and the 25 (34.2%) controls, were analyzed in this study. No statistically significant difference was determined between the groups in terms of age, height, weight or BMI. However, the weight gain in the VPA group was greater than that in the TPM group ($p = 0.022$).

Fasting insulin levels in the VPA group was higher than control group ($p = 0.029$). While first-hour postprandial insulin levels were higher in the VPA than TPM and control groups, they were lower in the TPM group than in the other two groups. A decrease was observed in second-hour postprandial insulin (insulin-2) levels compared to the first-hour values in all three groups.

Significant time-dependent change was determined in patients' glucose levels. First-hour postprandial glucose (glucose-1) was higher in the VPA group than in the TPM group. Postprandial glucose was still higher in patients receiving VPA at the end of the second hour. Time-dependent changes in blood glucose levels in the VPA group are shown in Fig. 1. Postprandial glucose levels were lower at 1 h in the TPM group compared to the VPA group. At the 2 h, however, glucose levels in the TPM group were similar. VPA group glucose-2 levels were also higher than those in the TPM and control groups. These differences were statistically significant.

Basal leptin (leptin-0) levels were higher in VPA group than TPM and control groups. Postprandial levels at 1 h were higher in the VPA group than in both the TPM and control groups ($p = 0.001$). Although postprandial levels at 2 h they were similar, this variation wasn't statistically significant.

Significant variation was determined between the groups in terms of NPY values (Table 5). Postprandial NPY levels were lower than fasting levels in the control group. It was similar in the TPM group. Fasting and postprandial NPY values were higher in both patient groups than those of the control group ($p = 0.000$). The elevation in the VPA group was greater than that in the TPM group.

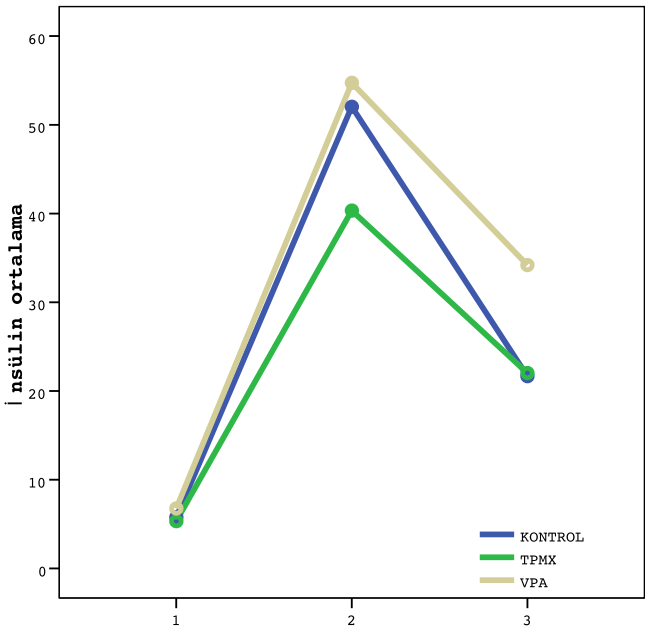


Fig. 1. Changes in insulin levels.

The time-dependent change in ghrelin values was statistically significant (p = 0.000).

No statistically significant difference was determined between the groups in terms of glucose-0, ghrelin-0, ghrelin-1 and ghrelin-2 values.

At two-way group comparisons, NPY-1 and NPY-2 values in the control group were lower than in the TPM and VPA groups (p = 0.000). Leptin-1 values were lower in the control group than in the VPA group (p = 0.001). Insulin-2, glucose-2, leptin-0 values in the VPA group were higher than in the control group and the TPM group (p = 0.000). NPY-0 values were higher than both of groups (p = 0.000). Insulin-1 values in the VPA group were higher than in the TPM group (p = 0.000). The results are summarized in Table 1.

4. Discussion

The hypothesis that AEDs, and particularly VPA, lead to weight gain, while TPM leads to weight loss is one supported by various studies. The weight gain in our patients receiving VPA throughout the study period was greater than that in the TPM group.

Examination of changes in insulin, glucose, leptin, NPY and ghrelin levels 1 and 2 h after a standard breakfast revealed a significant gradual change in insulin values. Insulin values in the VPA group rose at 1 h and decreased at 2 h, and were higher than in the control group and TPM group (Fig. 2).

The elevation in insulin values at hours 1 and 2 in the VPA group was statistically significant compared to both the control and TPM groups. The lowest median fasting insulin level in our study was observed in the control group, at 4.0. The equivalent value was 7.2 in the VPA group, significantly higher than that in the control group (p = 0.029). Low blood sugar levels not being observed despite the presence of high fasting and postprandial insulin levels in the VPA group is indicative of insulin resistance. When insulin resistance develops, more insulin needs to be released in order to maintain normal blood glucose levels. Hyperinsulinemia is a risk factor for diabetes mellitus. In one study, higher insulin levels and development of insulin resistance were reported in epilepsy patients receiving VPA therapy for 1 year and with weight gain compared to subjects with no weight gain. On the basis of these findings, it was suggested that VPA

Table 1
Comparison of insülin, glucose, leptin, NPY, Ghrelin levels between groups.

Group		Insulin-0	Insulin-1	Insulin-2	Glucose0	Glucose1	Glucose2	Leptin-0	Leptin-1	Leptin-2	NPY-0	NPY-1	NPY-2	Ghrelin-0	Ghrelin-1	Ghrelin-2
Control	Median	4,0	55,0	21,5	86,0	120,6	90,0	5,05	4,22	4,40	32,00	25,60	27,00	267,00	179,00	180,00
	25p	2,6	45,3	7,3	76,5	101,0	81,5	3,67	2,15	2,43	26,00	13,35	20,85	232,50	105,00	156,50
	75p	6,3	62,7	26,0	91,5	127,0	100,0	6,16	5,82	7,17	37,00	33,75	36,50	292,00	195,00	244,50
TPM	Median	5,1	40,0	20,3	81,0	101,0	90,0	5,80	6,00	5,60	45,00	43,00	45,00	267,00	189,00	189,00
	25p	3,5	33,6	15,3	80,0	91,0	80,0	3,20	3,89	3,71	32,00	36,00	34,00	206,00	134,00	167,00
	75p	6,3	48,3	25,9	89,8	119,0	93,0	8,10	7,70	8,00	55,00	56,00	55,00	334,00	200,00	245,00
VPA	Median	7,2	57,9	34,8	81,5	125,0	102,0	8,54	8,54	8,44	55,00	55,00	50,00	240,00	180,00	197,00
	25p	4,4	50,9	24,8	80,0	112,0	91,5	6,80	5,73	3,14	45,50	43,00	44,50	209,00	159,56	169,55
	75p	8,9	62,5	40,6	88,5	133,5	120,5	12,89	13,41	14,50	65,00	65,00	56,34	262,00	200,00	219,50
p		**0,029***	**0,000****	**0.000*****	**0,817**	**0,000*******	**0,000********	**0,001********	**0,001***	**0,090**	**0,000********	**0,000********	**0,000********	**0,126**	**0,557**	**0,963**

* The difference between the control group and VPA is significant.
** Significant difference in TPM group from control group and VPA group.
*** Significant difference in VPA group from both Topamax and Control group.
**** Comparison between Topamax and VPA was statistically significant.
***** Control group different from TPX and VPA group.

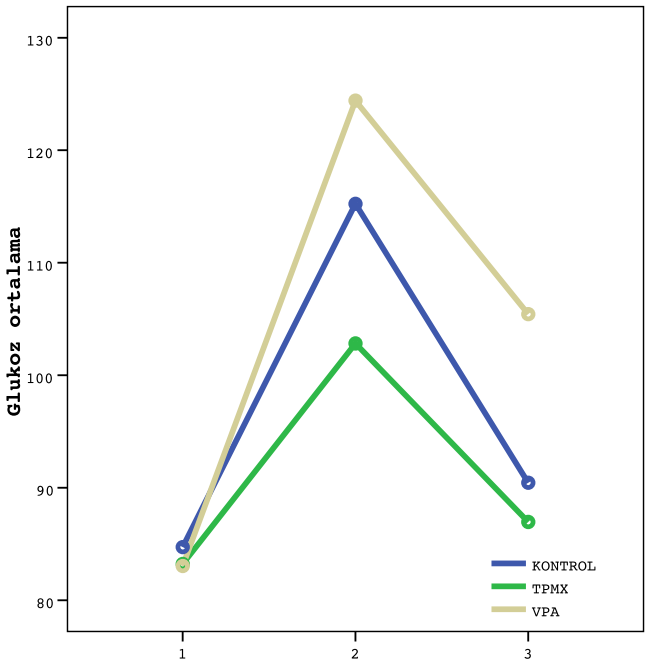


Fig. 2. Changes in patient and control group glucose levels.

does not alter insulin sensitivity directly, but does result in the development of insulin resistance [7].

Although numerous studies have been performed, the pathogenic mechanisms responsible for VPA-related weight gain are still not fully understood. Several hormones and cytokines involved in these mechanisms are still the subject of experimental and clinical research. In one randomized, controlled double-blinded study performed in order to investigate the effects of VPA on body weight, food intake, physical activity and hormones, Martin et al. [8] administered VPA or placebo to 52 healthy volunteers. Measurements performed at baseline and after 3 weeks revealed weight gain in the VPA group, but none in the placebo group. However, the changes in body weight between the groups were not statistically significant. VPA was shown to reduce glucose levels and to increase the motivation to eat. The authors suggested that VPA-related weight gain was not caused by change in physical activity or the hormones investigated [8].

Verrotti et al. [9] investigated the effect of VPA on weight gain in 114 children and adolescents with epilepsy and reported that obesity developed in 46 patients (40.4%) over a 2-year follow-up period. Metabolic syndrome was reported in 43.5% (n = 20) of these. Espinosa et al. [10] reported that the VPA-related weight gain effect in adolescents and adults was not observed in young children (<12 years). Monozygotic twins receiving VPA therapy were examined in order to assess the contribution of genetic factors to the weight gain effect of VPA. A similar weight course was observed in each pair of twins investigated in the study [11]. In one recent study, Stern et al. observed no change in weight, BMI, insulin, glucose, lipid or endocrine profiles in 57 girls with epilepsy receiving VPA therapy for a mean 3.2 years [12]. The same team also reported no endocrine or metabolic effects in boys using topiramate or VPA after approximately 1 year [13].

As our study results also indicate, VPA therapy is associated with increased insulin concentrations, particularly when this starts at an early age [14].

The low glucose and high insulin levels in this study, particularly in the VPA group, were interpreted in line with previous findings. Weight gain and associated insulin resistance were significant in the VPA group.

No significant change in body weight was observed in the patients receiving TPM therapy in our study. Although the mechanism involved is unclear, TPM is known to have a weight-reducing effect [15–17]. Klein et al. [18] determined a decrease in BMI in 59% of 22 epilepsy patients using TPM. Reiter et al. [19] examined changes in BMI in pediatric patients with epilepsy receiving long-term TPM therapy and also investigated weight loss predictors. A study of migraine patients using prophylactic TPM determined 7% weight loss over a 4-month period [20]. TPM has a specific effect in the reduction of food intake. This is probably due to antagonism on glutamatergic transmission in the lateral thalamus. Another possibility is that it causes weight loss by directly stimulating energy consumption [21].

The median fasting leptin value in the VPA group in this study was 8.54, higher than those in the TPM group (median 5.80) and the control group (median 5.05) (Table 1). In a study of 41 children with epilepsy, Sönmez et al. compared VPA and TPM groups and observed a significant weight increase in the children receiving VPA. Leptin levels were also high in the group with weight gain, but no insulin resistance was observed, even though high insulin levels were high [22]. Insulin and leptin exhibit different levels of mutual interaction. Hamed et al. [23] investigated serum leptin and insulin levels in children with epilepsy and examined risk predictors affecting weight gain. They reported that hyperinsulinemia and hyperleptinemia were more common in subjects using VPA compared to subjects not receiving treatment or else receiving carbamazepine, lamotrigine or VPA + lamotrigine. The increase in serum leptin levels was reported to be higher in subjects with weight gain than in those without. The authors also reported that leptin levels were correlated with age, BMI, VPA dosage and duration, and insulin levels. However, in our study, leptin levels were also high in the VPA group subjects with high insulin levels, even though there was no significant weight gain in the VPA group. We therefore think that leptin may be related to insulin resistance (Tables 2–4).

Fasting ghrelin levels were lower in the VPA group compared to the both of groups. However, no statistically significant difference was determined between group's ghrelin levels (Table 1). Ghrelin is known to stimulate food intake. However, meal-related ghrelin changes have not been well identified in children.

The idea of an increase in ghrelin levels in epileptic children using VPA is controversial [24]. Studies on the subject have reported inconsistent results, with ghrelin levels increasing in VPA users in some studies, but decreasing in others. We attributed the lack of a significant difference in ghrelin levels in our study to ghrelin principally reflecting BMI. VPA therapy in epileptic prepubertal children of normal weight was shown to reduce

Table 2
Comparison of insulin levels between groups.

Group		Insulin-0	Insulin-1	Insulin-2
Control	Median	4,0	55,0	21,5
	25p	2,6	45,3	7,3
	75p	6,3	62,7	26,0
TPM	Median	5,1	40,0	20,3
	25p	3,5	33,6	15,3
	75p	6,3	48,3	25,9
VPA	Median	7,2	57,9	34,8
	25p	4,4	50,9	24,8
	75p	8,9	62,5	40,6
	p	**0,029***	**0,000****	**0.000*****

* The difference between the control group and VPA is significant.
** Significant difference in TPM group from control group and VPA group.
*** Significant difference in VPA group from both Topamax and Control group.

Table 3
Comparison of glucose levels between groups.

		Glucose-0	Glucose-1	Glucose-2
Control	Median	86,0	120,6	90,0
	25p	76,5	101,0	81,5
	75p	91,5	127,0	100,0
TPM	Median	81,0	101,0	90,0
	25p	80,0	91,0	80,0
	75p	89,8	119,0	93,0
VPA	Median	81,5	125,0	102,0
	25p	80,0	112,0	91,5
	75p	88,5	133,5	120,5
	p	**0,817**	**0,000***	**0,000****

* Comparison between Topamax and VPA was statistically significant.
** The difference between VPA and Topamax and VPA and Control group was significant.

Table 4
Comparison of leptin levels between groups.

		Leptin-0	Leptin-1	Leptin-2
Control	Median	5,05	4,22	4,40
	25p	3,67	2,15	2,43
	75p	6,16	5,82	7,17
TPM	Median	5,80	6,00	5,60
	25p	3,20	3,89	3,71
	75p	8,10	7,70	8,00
VPA	Median	8,54	8,54	8,44
	25p	6,80	5,73	3,14
	75p	12,89	13,41	14,50
	p	**0,001***	**0,001****	**0,090**

* There is significant difference in VPA from control group and Topamax group.
** Significant difference between control group and VPA.

Table 5
Comparison of NPY levels between groups.

		NPY-0	NPY-1	NPY-2
Control	Median	32,00	25,60	27,00
	25p	26,00	13,35	20,85
	75p	37,00	33,75	36,50
TPM	Median	45,00	43,00	45,00
	25p	32,00	36,00	34,00
	75p	55,00	56,00	55,00
VPA	Median	55,00	55,00	50,00
	25p	45,50	43,00	44,50
	75p	65,00	65,00	56,34
	p	**0,000***	**0,000***	**0,000***

* Control group different from TPX and VPA group.

ghrelin levels in epileptic prepubertal children of normal weight compared to age- and weight-matched healthy individuals. On the basis of these findings, it may be concluded that ghrelin levels decrease independently of weight gain during epilepsy treatment [25].

Cansu et al. [26] observed 18 children newly diagnosed with epilepsy and started on VPA therapy over a period of 18 months. They compared weight, fasting glucose, insulin, leptin, NPY and ghrelin levels at the end of observation with those of a control group. No difference was determined in glucose and insulin levels. Aydin et al. [27] measured serum insulin, leptin and NPY levels in

Table 6
Comparison of Grelin levels between groups.

		Ghrelin-0	Ghrelin-1	Ghrelin-2
Control	Median	267,00	179,00	180,00
	25p	232,50	105,00	156,50
	75p	292,00	195,00	244,50
TPM	Median	267,00	189,00	189,00
	25p	206,00	134,00	167,00
	75p	334,00	200,00	245,00
VPA	Median	240,00	180,00	197,00
	25p	209,00	159,56	169,55
	75p	262,00	200,00	219,50
	p	0,126	0,557	0,963

20 epileptic children treated with VPA and determined increased mean BMI, insulin, a fasting insulin/glucose ratio and NPY levels and decreased glucose levels at the end of 3 months. The median fasting NPY level in our VPA group was 55, significantly higher than those in both the control group (median 32) and the TPM group (median 45) ($p = 0.000$). Due to this significant elevation in the VPA group, we think that NPY may be a hormonal marker indicating insulin resistance, similarly to leptin (Table 6).

Low blood sugar not being observed, even though high insulin levels are determined, in the fasting and postprandial periods in children with epilepsy receiving VPA monotherapy for at least 6 months, indicates insulin resistance. This is further supported by elevation in leptin and NPY levels in the VPA group. No significant difference was determined in terms of ghrelin levels in the VPA or TPM patient groups compared to the controls.

Understanding the effects of AEDs on body weight and the mechanisms involved, and regulating nutrition accordingly, is of great importance in terms of protecting against undesirable outcomes deriving from drug side-effects, particularly in growing children. Knowing the risk factors and the agents involved in side-effect mechanisms will be of assistance in patient monitoring and drug selection. In our study was investigated the effects of weight gain with effects of hormon with antiepileptic therapies. The some features like this eating habits, sports habits were unknown when choosing groups. This was the weakness point of our study. Patients were selected among the follow-up patients in our polyclinic. This study would have been a much more strong if the study was planned as a regular period of weight measurement and hormonal measurements after the first diagnoses. We think that further, wider-ranging studies are now needed in order to fully elucidate these mechanisms.

An author agreement/declaration

All authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere. All authors have declared that they have no conflict or interest.

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