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Evaluation of the body composition with bioelectrical impedence analysia in epileptic patients treated with valproic acid

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Abstract

The aim is to examine the effects of valproic acid on the metabolic parameters, body composition and anthropometric measurements. Non-obese patients diagnosed with idiopathic epilepsy were included in the study. Multifrequency bioelectrical impedance analysis, anthropometric measurements, fasting glucose, lipid levels, serum insulin levels and thyroid function tests were evaluated at the beginning, third and sixth months of valproic acid treatment. A total of 25 patients were investigated. The mean age of patients was 8.21±3.96 years. The body mass index of patients significantly increased during treatment. Fat mass, lean mass, basal metabolism rate, body fat mass index and fat free mass index values significantly increased and basal metabolism rate/body weight ratio significantly decreased during valproic acid treatment. Significant increase in thyroid stimulating hormone levels and significant decrease in free thyroxine levels occurred during the treatment.
Conclusion: valproic acid leads to weight gain by both increasing fat and lean mass.

Keywords: Multifrequency bioelectrical impedance analysis; epilepsy; valproic acid; weight gain; children.

INTRODUCTION

Valproic acid is one of the most commonly used antiepileptic drugs because of its wide spectrum of antiepileptic activity for different types of seizures. It has been suggested that valproic acid increases gamma amino butyric acid synthesis and reduces the epileptogenic gamma-hydroxybutyric acid levels.[1]

Valproic acid is an effective antiepileptic agent for generalized and partial seizures. Although the side effect profile of valproic acid is low, severe side effects including Reye's syndrome, hepatic steatosis, pancreatitis and hematologic abnormalities have also been reported.[2,3] One of the most disabling side effects of valproic acid treatment is the weight gain. Reported rate of weight gain varies from 40% to 60%.[4,5] Metabolic and endocrine abnormalities underlying the mechanisms of weight gain are still not fully understood.[6,7] Recently, Kanemura *et al*.[8] suggested that an increase in serum insulin and insulin/glucose levels may cause weight gain possibly by stimulating appetite.

Although weight gain during valproic acid treatment is well known, few prospective studies have investigated long term metabolic effects and changes in body composition. The aim of this study is to prospectively examine the changes in anthropometric, body composition and metabolic measurements in epileptic children treated with valproic acid.

METHODS

This study took place at Pediatric Neurology Department of Dokuz Eylul University (İzmir/Turkey). Non-obese children with newly diagnosed idiopathic epilepsy, between August 2016 and June 2017 were included in the study. Patients with psychomotor retardation, symptomatic epilepsy, chronic neurologic disease, abnormal neurologic examination or obesity at the onset of treatment were excluded from the study. Multifrequency bioelectrical impedance analysis, anthropometric measurements and laboratory examinations were evaluated at the beginning, third and sixth months of the treatment. All measurements were taken in the morning, between 8 and 10, after a fast of at least 8 hours and they were not allowed to take

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any water prior to the examination. Informed consent was obtained from each patient.

Multifrequency bioelectric impedance analysis

By the multifrequency bioelectric impedance analysis, an alternating electrical current of constant frequency with low intensity is applied to body. Body composition and body water compartment analysis were assessed by determining the resistance, reactance, and impedance with a Bodystat Qudscan 4000 bioimpedance analyzer (Bodystat Limited, British Isles). Current-detecting electrodes were placed between the styloid processes of the right radius and ulna and between the medial and lateral malleoli of the right ankle. Current-introducing electrodes were then placed on the respective dorsal surfaces of the metacarpals and metatarsals, 5 cm distal to the proximal electrodes. Total body water, extracellular water, intracellular water, extracellular water / intracellular water ratio, fat percentage, fat mass, lean, body fat mass index, fat free mass index, basal metabolism rate were evaluated.

Anthropometric measurements: Body mass was determined on a SECA balance scale (Hamburg, Germany) to the nearest 0.1 kg, with subjects dressed in a light t-shirt and shorts. Body height of the patients was recorded on a stadiometer with a standing subject to the nearest 0.1 cm with a Harpenden fixed stadiometer (Holtain Ltd., Crymych, Dyfed, Britain). Body mass index was calculated as weight/height2 (kg/m2). Circumferences (waist, hip) were measured. Waist/hip ratios were also evaluated. Obesity and overweight status were defined according to International Obesity Task Force cutoff values.[9]

Laboratory analysis

After a fast of at least 8 hours, blood levels of total cholesterol, triglycerides, lowdensity and high-density lipoprotein cholesterol, fasting glucose, insulin and serum free triiodothyronine, free thyroxine and thyroid stimulating hormone levels were assessed quantitatively before and after 3 and 6 months of valproic acid treatment. The homeostasis model assessment index for insulin resistance was calculated according to the following equation: (fasting insulin (U/m) × fasting glucose (mmol/L))÷22.5.[10]

Fasting plasma glucose, serum triglycerides, total cholesterol, and high-density lipoprotein cholesterol concentrations were measured enzymatically using DP Modular Systems (Roche Diagnostic Corp., Indianapolis, IN). Low-density lipoprotein levels were calculated using the Friedewald formula when plasma triglycerides were <400 mg/dL. Plasma insulin was measured according to the electrochemiluminescence immunoassay method, using an automated immunoassay analyzer (Immulite 2500 Insulin, Diagnostic Products Corporation, Los Angeles, CA). Free triiodothyronine and free thyroxine levels were measured using an immunoassay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, Calif., USA). Thyroid stimulating hormone was measured with a chemiluminescence immunometric assay (Immulite 2000 Diagnostic Products Corporation). Serum valproic acid levels were measured using fluorescent polarization immunoassay (Cobas Integra 800, Roche Diagnostics, Basel, Switzerland).

Statistical methods

Data were analyzed with Statistical Package for the Social Sciences, Version 15.0. was used for statistical analyses. Repeated-measures analysis of variance was used to compare clinical and metabolic parameters before and after 3 and 6 months of valproic acid treatment. When repeated-measures analysis of variance resulted in a significant difference ($P < 0.05$), a paired-sample t test was used to detect the group that created the statistical significance. A pvalue < 0.05 was considered statistically significant. All data are expressed as mean standard deviation.

RESULTS

A total of 33 patients were included in the study. Five patients did not complete the study and three patients were excluded because they required other antiepileptic drugs due to poor seizure control with valproic acid treatment. Among the 25 patients who completed the study, 17 (68%) were male and 8 (32%) were female. 12 patients (4 girls and 8 boys; 48 %) were prepubertal and 13 patients (4 girls and 9 boys; 52 %) were pubertal. The mean age of patients was 8.21±3.96 years (range 3.2-15.3 years). Treatment related side effects were seen in 3/25 (12%) of the patients, one patient had hair loss and two patients developed slightly elevated liver enzymes during the treatment.

The body mass index of patients significantly increased during treatment (body mass index, 17.22±2.73 (0.6 ± 0.13 SDS), 18.63±3.42 (1.1 ± 0.16 SDS) and 18.48±3.68 (1.0 ± 0.18 SDS), p=0.001). Statistical significance was evident regarding body mass index before and after three

months of treatment and also before and after six months of treatment (p<0.001 and p=0.006, respectively). However, there was a slight decrease in the body mass index at six months of treatment when compared with the values of third month, which was not significant (body mass index, 18.63±3.42 to 18.48±3.68, p=0.377). Waist/hip circumferences ratio of patients did not significantly differ during treatment (waist/hip ratio, 0.84±0.6, 0.86±0.5 and 0.84±0.49, p=0.171) (Table 1).

Multifrequency bioelectric impedance analysis showed similar values of total body water, extracellular water/ intracellular water and fat percentage before and after three and six months of treatment. In contrast, basal metabolism rate, body fat mass index and fat free mass index values of patients significantly increased and basal metabolism rate /body weight ratio significantly decreased during treatment (p<0.001, p=0.024, p=0.004 and p<0.001, respectively). Statistical significance was evident regarding basal metabolism rate, basal metabolism rate / body weight, body fat mass index and free mass index before and after three months of treatment (p<0.001, p<0.001, p=0.012 and p=0.010, respectively). Although statistical significance was evident for basal metabolism rate, basal metabolism rate / body weight and fat free mass index before and after six months of treatment (p<0.001, p<0.001 and p=0.004, respectively), body fat mass index values did not significantly differ between the initial and six month values (p=0.160). Statistical significance was also evident for fat and lean mass before and after three and six months of treatment (p=0.004 and p<0.001, respectively) (Table 1).

There was no significant difference between prepubertal and pubertal group regarding total body water, extracellular water/intracellular water, basal metabolism rate, basal metabolism rate/body weight, fat percentage, fat mass and lean mass. But Δ body mass index (0 to 6 months), Δ body fat mass index (0 to 6 months) and Δ fat free mass index (0 to 6 months) levels were significantly increased in the pubertal group (p=0.001, p=0.036 and p=0.014, respectively). These parameters were not significantly differ between male and female patients.

Regarding the laboratory examinations, a significant increase was present in thyroid stimulating hormone levels before and after three months of treatment and also before and after six months of treatment (p<0.001 and p<0.001 respectively). However, thyroid stimulating hormone levels of patients did not significantly differ between the three and six months of the treatment (p=0.911). There was also a statistically significant decrease in free thyroxine levels before and after three months of treatment (p=0.005). However, free thyroxine levels did not differ between before and six months of treatment and also three and six months of treatment (p=0.09 and p=0.5, respectively). There was no significant difference in free triiodothyronine levels during treatment (p=0.395). Although there were a statistically significant difference according to thyroid stimulating hormone levels

Table 1: Anthropometric and MFBIA parameters of patients

	0 month	3 month	6 month	p
BMI (kg/m²)	17.22±2.73	18.63±3.42	18.48±3.68	**0.001**
Waist/Hip	0.84±0.6	0.86±0.5	0.84±0.49	0.171
TBW%	61.9±6.7	59.94±6.42	60.97±5.18	0.087
ECW/ICW	0.92±0.19	0.89±0.16	0.87±0.14	0.076
BMR (kcal)	1144.9±284.1	1197.22±286.72	1227.5±302.07	**<0.001**
BMR/BW	41.55±9.33	39.61±8.86	38.60±9.07	**<0.001**
BFMI	3.39±1.99	4.19±2.3	3.86±2.05	**0.024**
FFMI	13.83±1.96	14.44±2.16	14.61±2.33	**0.004**
Fat%	19.18±9.1	21.64±8.62	20.25±6.96	0.115
Fat mass (kg)	5.58±4.01	7.18±5.01	6.98±4.48	**0.004**
Lean (kg)	24.88±12.98	25.99±12.33	28.27±13.88	**<0.001**

MFBIA: Multifrequency bioelectrical impedance analysis, BMI: Body mass index, TBW: Total body water, ECW: Extracellular water, ICW: Intracellular water, BMR: Basal metabolism rate, BW: Body weight, BFMI: Body fat mass index, FFMI: Fat free mass index

and free thyroxine levels, the differences were not clinically significant and none of the patients need to be treated. There were no differences in fasting glucose, serum insulin levels, homeostasis model assessment index for insulin resistance and lipid profiles before and after three and six months of treatment (Table 2).

Mean dosages (mg/kg/day) of valproic acid at the beginning, three months and six months of treatment were 14.36±1.55, 16.72±2.15 and 17.44±2.52, respectively. There were no differences in serum levels of valproic acid (μg/mL) at the 15th day and after three and six months of valproic acid treatment (serum levels of valproic acid, 52.5±5.4, 56.82±3.76 and 56.38±4.7, respectively, p=0.789) (Table 2).

DISCUSSION

Weight gain is the most common adverse effect of valproic acid treatment. The reported rate of weight gain differs in various clinical investigations.[4,9] Valerio *et al*. reported that risk factors associated with weight gain with valproic acid treatment include increased dosages, female gender and generalized seizure type.[10] Mechanisms that have been proposed for valproic acid related weight gain include increased leptin levels and insulin levels, decreased gluconeogenesis and β-oxidation of fatty acids.[7,10] Rauchenzauner *et al*.[6] reported that epileptic children treated with valproic acid had higher leptin concentrations, body mass index, body fat, serum insulin concentrations and homeostasis model assessment index for insulin resistance when compared with the children treated with antipileptics other than valproic acid. Another prospective study evaluating metabolic alterations during valproic acid treatment found that body mass index and body mass index standard deviation scores of patients increased significantly during treatment. Although there was no statistical significance regarding fasting glucose, serum insulin, triglyceride, and high-density lipoprotein cholesterol levels and the homeostasis model assessment index for insulin resistance, a statistically significant increase in total and low-density lipoprotein cholesterol levels had occurred after 12 months of valproic acid treatment [7]. Although the body mass indexes of our patients significantly increased during valproic acid treatment, we found no significant increases regarding fasting glucose, serum insulin levels, homeostasis model assessment index for insulin resistance and lipid profiles before and after three and six months of treatment.

Previous studies showed that valproic acid associated weight gain was most evident in the first six months of treatment.[7,11] The body mass index of our patients significantly increased during the first three months of treatment, but a slight decrease occurred between the third and six months of treatment (body mass index, 17.22±2.73 (0.6 ± 0.13 SDS), 18.63±3.42 (1.1 ± 0.16 SDS) and 18.48±3.68 (1.0 ± 0.18 SDS) , p=0.001). We found no change in waist/hip circumferences ratios of patients during treatment.

Table 2: Metabolic parameters of patients

	Pretreatment	Three months after treatment	Six months after treatment	P
Glucose (mg/dL)	91.48±11.87	91.74±12.01	85.05±10.45	0.115
Insulin (μU/ml)	4.19±2.60	5.79±5.49	4.05±3.75	0.355
HOMA-IR	1.02±0.73	1.44±1.54	0.85±0.95	0.740
ft3 (pg/mL)	4.43±1.14	4.51±0.74	4.42±0.94	0.395
ft4 (ng/dL)	1.14±0.19	1.02±0.10	1.08±0.16	**0.032**
TSH (IU/ml)	1.98±1.08	3.24±1.51	3.19±1.28	**<0.001**
Cholesterol (mg/dl)	158.33±24.64	160.33±26.52	156.35±29.42	0.692
Triglycerides (mg/dl)	92.95±49.16	89.14±42.34	75.00±30.18	0.432
LDL (mg/dl)	93.43±19.66	92.52±24.09	95.74±23.26	0.911
HDL (mg/dl)	46.33±11.55	49.95±9.27	45.57±9.30	0.961
Valproate dosage (mg/kg)	14.36±1.55	16.72±2.15	17.44±2.52	**<0.001**
Serum levels of valproate (μg/mL)	52.5±5.4	56.82±3.76	56.38±4.7	0.789

HOMA-IR: Homeostasis model assessment index for insulin resistance, ft3: Free triiodothyronine, ft4: Free thyroxine

In childhood, valproic acid treatment may lead to endocrine and metabolic alterations abnormalities including hyperinsulinism, hyperandrogenism, changes in lipid and thyroid hormone profiles.[12-14] Increase in thyroid stimulating hormone levels and decrease in free thyroxine levels have been reported in children treated with valproic acid.[14,15] The underlying mechanisms of alterations in serum thyroid hormone levels have not been understood. In our study, in accordance with the literature, we found a significant increase in thyroid stimulating hormone levels and decrease in free thyroxine levels but the differences were not clinically significant and none of the patients need to be treated.

There are few studies in the literature investigating the body composition of patients treated with valproic acid.[6,16,17] Rauchenzauner *et al*.[6] detected higher body fat percentages and fat mass in valproic acid treated patients compared with nonvalproate group. However, their cross sectional cohort study included obese and nonobese patients together. El-Khatib *et al*.[16] concluded that female patients treated with valproic acid expressed higher percentage of body fat than male patients. Another cross sectional cohort study evaluating the body composition in patients treated with valproic acid for at least six months found higher fat percentage and fat mass when compared with non valproic acid treated and healthy control groups.[17] In our prospective study, only nonobese patients were included and the results of the multifrequency bioelectrical impedance analysis at three and six months of treatment were compared with the baseline parameters. In contrast to previous studies, multifrequency bioelectrical impedance analysis showed similar values of fat percentage before and after three and six months of treatment. However, fat and lean mass basal metabolism rate, body fat mass index and fat free mass index significantly increased during treatment. These results suggest that valproic acid stimulates weight gain by both increasing fat and lean mass. Valproic acid also acts on the hypothalamus and changes the secretion profile of hormones like corticotropin releasing factor.[18,19] It has also direct effects which lead to increased appetite and thirst 6. One may also suggest that this hypothalamic dysregulation may lead to changes in the body fluid compartments. In our study we found no changes in total body water values and extracellular water/intracellular water ratio during valproic acid treatment.

In conclusion, valproic acid treatment leads to weight gain by both increasing fat and lean mass. Patients treated with valproic acid should be regularly followed for thyroid dysfunction. Multifrequency bioelectrical impedance analysis may be a useful technique to detect body composition changes during valproic acid treatment but more studies are needed to clarify how valproic acid changes body composition.

DISCLOSURE

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