The effect of valporate therapy on body weight and serum leptin level in children with epilepsy

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ABSTRACT

Background: Valproic acid is a broad-spectrum antiepileptic drug used for the management of partial and generalized seizures, bipolar disorders, and migraine prophylaxis. Valproic acid treatment reportedly causes metabolic adverse effects, the most frequent of which is weight gain. The goal of this work is to study the effect of valporate therapy on body weight and serum leptin in children with epilepsy.

Methods: This prospective case control study was done in Pediatric neurology clinic, Pediatric Department, in Benha University Hospital. And was conducted on 60 child divided into 2 groups (Group 1) study group and (Group 2) control group. All subjects were subjected to (full history taking, complete clinical assessment and laboratory investigation including serum leptin).
**Results:** There was a highly statistically significant increase in serum leptin in children treated with valporate compared to healthy controls. Also body weight and body mass index increased significantly.

**Conclusion:** VPA causes weight gain that is possibly due to multiple endocrinologic mechanisms like increase lipiten level. However, it is difficult to select candidates susceptible to weight gain prior to treatment.

**Key words:** valporate therapy – serum leptin – body weight.

1- **Introduction:**

Valproate (VPA) is one of the most frequently prescribed antiepileptic drugs worldwide. (1)

To our knowledge, no study evaluating valproic acid associated weight gain specifically included only young children. In young children, measures of BMI alone are inappropriate for comparisons of overweight and obesity, as they change with age. On that basis, changes in the age- and sex-specific BMI z-scores were analyzed as a continuous variable, using the mixed-effects model. (2)

The exact mechanisms of weight gain in patients taking valproic acid remains to be established, but several potential mechanisms have been suggested. Although genetic factors may play a role, lowered blood glucose levels have been proposed as one cardinal mechanism by which valproic acid may lead to obesity. Indeed, low glucose levels stimulate eating through an effect on glucose-responsive neurons in the medial hypothalamus, which, in turn, reduces the efferent inhibitory output to the lateral hypothalamus (3)

Valproic acid (VPA) is an acidic compound that is commonly used as an anticonvulsant and mood-stabilizing agent in the treatment of epilepsy, mania and bipolar disorders as well as the prevention of migraine headaches. The
VPA is prescribed based on the patient’s clinical response and the serum level of drug. Although there is not enough data about the therapeutic range for unbound VPA, but it is generally accepted that the therapeutic range of VPA for the treatment of epileptic patients is 50 to 100 µg/mL.(4)

Various mechanisms have been proposed to explain the weight gain associated with VPA treatment. An increased consumption of food and energy-rich beverages because of an increased appetite and abnormal thirst has been suggested.(5)

The mechanism by which VPA increases body weight is not understood. The balance between energy intake and expenditure influences body weight; therefore, VPA may alter energy intake, physical activity (PA) energy expenditure or both. Alterations in energy intake or expenditure can result from, or be associated with, changes in biological mechanisms, including hormone levels.(6)

Regulation of body weight Much is known about the control of body weight. Some mechanisms for weight control implicate pathways, neurotransmitters, and receptors that could be influenced by AEDs. The control of body weight and mass involves multiple mechanisms. Body weight changes depend on the balance of caloric intake and energy expended. The brain integrates information from many afferent inputs and circulating factors to regulate food intake and energy expenditure.(7)

Serum leptin is correlated with the percentage of body fat. Two areas of the hypothalamus integrate the afferent signals to regulate feeding patterns: the lateral hypothalamus and the medial hypothalamic nuclei. Caloric balance may be altered, with ventromedial lesions causing hyperphagia and lateral hypothalamic lesions producing a syndrome of aphagia and weight loss in experimental animals.(8)

The goal of this work is to study the effect of valproate therapy on body weight and serum leptin in children with epilepsy.
2- Subjects and Method

This prospective case control study was done in Pediatric neurology clinic, Pediatric Department, in Benha University Hospital. And was conducted on 60 child divided into 2 groups:

**Group 1 (study group):** This study will be conducted on 30 patients collected from the Pediatric neurology clinic, Pediatric Department, in Benha University Hospital. **Group 2 (control group):** 30 healthy subjects' age & sex matched.

**Inclusion criteria:** children (age ranged between 5 and 10 years), they were with a history of new-onset seizures and in need of treatment with valproate, both sex will be included, and patients receive valporate drug.

**Exclusion criteria:** Patients with symptoms and signs of chronic illnesses other than epilepsy (e.g. endocrine, metabolic, hepatic, or renal diseases), a history of status epilepticus, previous use of drugs affecting body weight (e.g : topiramate), and overweight (BW more than 97th percentile for age & sex).

The study was approved by local Ethics Committee of Benha faculty of medicine and informed written consents were taken from parents of the included subjects prior to be involved in the study.

A standardized data sheet was utilized to record patients history, clinical examination and investigations that were performed, as follows: Full history taking, Full clinical examination, Laboratory investigation.

Blood samples will be obtained at 8 a.m. after an overnight fast for 10 hours for the analysis of serum leptin. The analyses will be done before the initiation of therapy, at the 4th month of the therapy and after 8 months from start of the therapy. Serum leptin: leptin concentrations will be analyzed with an enzyme-amplified sensitivity immunoassay using kits from BioSource Co.

Under sterile aseptic techniques 5 ml of venous blood were withdrawn from the patient by the pediatrician. The blood sample was centrifuged after
clotting for 10 minutes at 3000 rpm in for separation of the serum. serum was separated, divided into aliquots and kept at -20 °C till analyzed.

The data were coded, entered and processed on computer using SPSS (version 18). The results were represented in tabular and diagrammatic forms then interpreted. Mean, standard deviation, range, frequency, and percentage were used as descriptive statistics.

3- Results:

This study was conducted at Benha University hospital, Pediatric department, on 30 patients receiving valproate therapy and 30 healthy controls. There were no significant differences between cases and controls as regard to age and sex.

There were no significant differences between cases and controls as regard to baseline measures before treatment by valproate which included head circumference (P value = 0.949), weight (P value = 0.384), BMI (P value = 0.252) and serum leptin (P value = 0.917) (Table 3)

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<td>BMI</td>
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<td>15.97 ±0.61</td>
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<td>Leptin (ng/ml)</td>
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HC = Head circumference            BMI = Body Mass Index
Effect of valproate therapy in cases and controls at the 4th month of the therapy (baseline) and after 8 months from start of the therapy Was as following:

At 4 months the therapy: There were no significant differences between cases and controls as regard to weight, BMI and serum leptin.

At 8 months the therapy: Weight, BMI and serum leptin showed statistical significant differences between cases and controls.

Mean weight in cases was higher (29.9 kg) than mean weight in controls (26.25). This was statistically significant (P value = 0.012). Mean BMI in cases was higher (16.9) than mean BMI in controls (16.18). This was statistically significant (P value = 0.009).

Serum leptin. Mean serum leptin in cases was higher (2.4 ng/ml) than mean serum leptin in controls (0.8 ng/ml). This was statistically significant (P value <0.001).

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<th>Table (2) : Weight, BMI and serum leptin at 4 &amp; 8 months in both groups</th>
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<td><strong>Weight (kg)</strong></td>
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<td><strong>Leptin (ng/ml)</strong></td>
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|*Summarized as median and range.
3- Discussion:

Weight gain is one of the most common adverse effects with VPA as it has been described in several studies (9). This cosmetic condition is compounded by the high prevalence of depression among epileptic patients. (10) Weight gain not only affects body image and self-confidence with adverse psychological effects leading to non-compliance to medications, (11)

Obesity also associated with pathologic consequences related to obesity as reproductive disorders, dyslipidemia, hypertension, insulin resistance, diabetes mellitus and atherosclerosis and its related vascular complications. (12)

The two common homeostatic hormones, insulin, a protein product of pancreatic b-cells and leptin, a protein product of adipocytes, (13) have been expected to form a common link to weight gain in epilepsy with the use of some AEDs. (14) In general, normally, they act together to balance food intake and energy expenditure. (15) Data regarding the effect of various AEDs on insulin and leptin levels are controversial. (16) Furthermore, mechanisms of AEDs-induced alteration in insulin and leptin metabolisms have not been well described. Factors such as increased food intake and insulin resistance have been suggested to enhance plasma leptin levels and subsequently tissue leptin resistance. (17)

In previous studies, the increase in body mass index and weight gain was reported to occur within 3 months of initiation of the treatment, occurring in approximately 40% of children. (18)

Leptin is a product of the OB gene, which was first detected in mice and is considered to be a signal factor that regulates body weight and energy expenditure. (19)

It is likely that leptin regulates body weight through neuropeptide Y, which stimulates food intake and decreases thermogenesis in the hypothalamus. A strong correlation has been observed between serum leptin concentrations,
body mass index, and body fat mass in humans. This suggests that obesity might be associated with a decreased sensitivity to leptin. Because valproate can induce weight gain, high levels of serum leptin can be expected. In accordance with the literature, (20)

The hypothesis that VPA, lead to weight gain and increase Leptin hormone is supported by various studies (21). 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 (22).

The present study is in the same line, shows statistical significant differences between case and control in weight, BMI, Serum leptin level, while a marked increase is noticed to this variants.

This results justified with Rehman et al., who reported that Sodium VPA is associated with significant rise of BMI, hyperinsulinemia, raised insulin resistance, and increased leptin levels in children with epilepsy (23).

Also this result similar to Nafiye et al, who exemplified that studied the effects of valproate and topiramate use on serum insulin, leptin, neuropeptide y and ghrelin levels in epileptic children. (24)

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. (25)

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 (26).

Verrotti et al. 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. (27)

The precise mechanisms underlying the VPA-associated weight gain, however, remains unclear. 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 (28).

VPA-treated patients developed increased appetite, thirst, and quenching with calorie-rich beverages. All these behaviors indicate toward hypothalamic stimulation. More recently, a study carried out in Wistar strain female rat shows that treatment with VPA disrupts hypothalamic axis at the level of GnRH pulse generator. (29)

Weight gain is also attributed to VPA-induced changes in insulin and leptin levels. Insulin level and insulin resistance (HOMA-IR) were significantly elevated in the treatment group in comparison to control in this study. VPA is a fatty acid derivative, and this increase in free long chain fatty acid dysregulates the action of insulin and promotes the onset of insulin resistance through the inhibition of various metabolic pathways such as glucose uptake, glycogenesis, and the glucose oxidation. (30)

Serum insulin is also thought to be increased due to the inhibition of hepatic insulin metabolism by VPA. Increased insulin levels were also proposed to be due to the direct action of VPA on beta cells of the pancreas. (31)
Leptin, a hormone secreted by adipose tissue, acts primarily to regulate body weight and energy expenditure. 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 (32).

Serum leptin levels were significantly raised in patients on VPA group in our study. Similar results were reported in studies done by Verrotti et al. (33) They demonstrated that after 1 year of VPA treatment, obese patient had significantly higher leptin levels as compared to controls.

Finally we recommend that while managing children with epilepsy, neurologists should keep in mind the differential effect of long-term use of various antiepileptic medications on patients weight and lipid metabolism. VPA causes weight gain that is possibly due to multiple endocrinologic mechanisms. However, it is difficult to select candidates susceptible to weight gain prior to treatment.
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