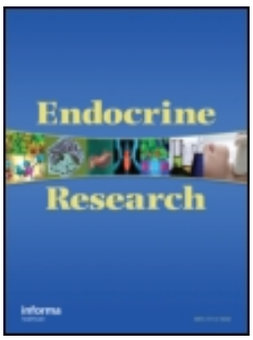
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The Effects of Oxcarbazepine and Valproate Therapies on Growth in Children with Epilepsy

Ali Cansu[1], Ediz Yesilkaya[2], Ayse Serdaroglu[3], Orhun Camurdan[4], Tugba Luleci Hirfanoglu[3], Abdulbaki Karaoglu[2], Aysun Bideci[4], and Peyami Cinaz[4]

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Aim. This study aimed to evaluate the effects of monotherapy with valproate or oxcarbazepine on the linear growth of children with idiopathic epilepsy. *Methods*. Antiepileptic treatment with valproate or oxcarbazepine was initiated in 76 patients. These were evaluated at baseline and at 6 and 18 months after commencement of therapy to determine height standard deviations (height z-scores). Serum ghrelin, insulin-like growth factor-1, and insulin-like growth factor-binding protein-3 levels were measured. *Results*. In prepubertal patients receiving oxcarbazepine, height z-scores were elevated after 6 and 18 months of therapy ($p = 0.008$ and $p = 0.001$, respectively); in pubertal patients, a significant increase was noted at the 18th month of therapy ($p = 0.004$). In prepubertal patients receiving oxcarbazepine, serum standardized insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels were significantly higher at the 18th month of therapy compared with baseline ($p = 0.005$ and $p = 0.004$, respectively). In pubertal patients receiving valproate, serum ghrelin levels were significantly decreased at the 18th month of therapy compared with baseline ($p = 0.006$). *Conclusion*. Exposure to oxcarbazepine stimulated linear growth in epileptic patients through mechanisms involving the release of insulin-like growth factor-1 and insulin-like growth factor-binding protein-3. In contrast, exposure to valproate did not affect linear growth, but did lead to a decrease in serum ghrelin levels.

Keywords Antiepileptic drugs, Growth, Weight, Insulin-like growth factor-1, Ghrelin, Epilepsy

INTRODUCTION

Despite the significant effects on growth factors such as weight, sex hormone status, general nutrition, genetic potential, and inflammation, the growth hormone insulin-like growth factor-1 axis is the main regulator of postnatal growth (1). Plasma concentrations of insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 are indicators of endogenous secretion of growth hormone. This makes them useful parameters for assessing the rate of growth (1).

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The relationship between valproate and oxcarbazepine use and endocrine disorders has been well described, particularly with regard to weight gain, thyroid hormone alterations, the reproductive system, and bone metabolism (2–9). However, there have been few studies concerning the effects of valproate and oxcarbazepine on growth in children (10–14). Some, but not all (14), of these have reported that valproate therapy negatively affects growth (12,15,16) and leads to a decrease in serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels (13). These studies have also stressed valproate use over the long term can affect final height (12,15,16). On the other hand, the small numbers of studies on the effects of oxcarbazepine on children growth have reported increased insulin-like growth factor-1 levels in patients receiving oxcarbazepine therapy before puberty, compared with control (10). However, the final heights of patients receiving oxcarbazepine therapy before puberty were similar to those of the control patients (10,14).

Ghrelin is an endogenous growth hormone-releasing peptide predominantly produced by the stomach, although substantially lower amounts are also produced in the hypothalamus. Growth hormone secretagogue receptors mediate its release (17). A relationship is known to exist between ghrelin and insulin-like growth factor-1/insulin-like growth factor-binding protein-3 metabolism (18). Increased (13,14) and decreased (19,20) levels of ghrelin have been reported in patients receiving valproate and carbamazepine. However, there is only one study reporting the impact of OXC treatment on serum ghrelin levels (21).

To the best of our knowledge, there are very few prospective studies on the effects of valproate and oxcarbazepine therapy, investigating the relationship between physical growth, insulin-like growth factor-1, insulin-like growth factor-binding protein-3, and ghrelin in prepubertal and pubertal children with epilepsy. We therefore aimed to evaluate the effects of monotherapy with valproate or oxcarbazepine on linear growth in children with newly diagnosed idiopathic epilepsy.

METHODS

The study was conducted at Gazi University, Department of Pediatric Neurology, in accordance with the Declaration of Helsinki, International Conference on Harmonisation—Good Clinical Practice guidelines, and local regulations. The study was approved by the local ethics committee.

Patients and Study Design

Totally 76 newly diagnosed pediatric patients ranging in age from 2 years, 8 months to 16 years, and 7 months started on antiepileptic drug therapy for idiopathic epilepsy at the Gazi University, Department of Pediatric Neurology and were included in the study. Patients were not receiving any other antiepileptic drugs or any drug that might affect endocrine metabolism (e.g., growth hormone or thyroid hormone), and were ambulatory, and had no diagnosed neurological deficit or any renal, thyroid, hepatic, cardiac, or neurometabolic disease or any other chronic disease. Diagnostic screening test results (cranial magnetic resonance imaging, tandem-mass spectrophotometry, and amino acid and organic acid screening in blood and urine) were normal. Patients with neurological deficits or anomalies, or hypothyroidism, indicated by high levels of thyroid-stimulating hormone and low levels of thyroxine were excluded.

During patient recruitment, one patient was diagnosed with a cortical abnormality based on cranial magnetic resonance imaging findings and was thus excluded. Three patients were excluded due to diagnosis of subclinical hypothyroidism (basal serum thyroid-stimulating hormone of >5 μIU/mL and normal serum thyroxine levels),

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and one was excluded due to a ventricular septal defect. One prepubertal patient receiving oxcarbazepine, one prepubertal patient receiving valproate, and two pubertal patients receiving valproate withdrew their consent for treatment. Eleven patients with resistant seizures (three prepubertal patients and one pubertal patient receiving oxcarbazepine, and four prepubertal and three pubertal patients receiving valproate) were excluded due to the use of a second antiepileptic drug at different stages of the study.

Epilepsy was defined as two or more afebrile seizures, not occurring within a 24 h period and not associated with acute central nervous system insult. Seizure type was classified according to the criteria established by the International League against Epilepsy (22). The antiepileptic drug dose was determined on the basis of generally accepted guidelines (23). Either oxcarbazepine or valproate was commenced, on an alternate basis, in patients with partial epilepsy, while valproate was used for all patients with primary generalized epilepsy. Oxcarbazepine and valproate were administered twice daily. Overall, 36 (18 girls and 18 boys) patients with a mean age of 8.1 ± 4.0 years were started on oxcarbazepine therapy, while the remaining 40 (22 girls and 18 boys) patients, with a mean age of 10.0 ± 4.2 years, were started on valproate therapy. Of the 40 patients started on valproate therapy, the diagnosis was idiopathic partial epilepsy in 24 and primary generalized epilepsy in 16.

The pubertal status of the patients was assessed following the method described by Marshall and Tanner (24,25). Each patient was examined by the same physician at baseline and at the 6th and 18th months of antiepileptic drug therapy. Heights were measured to the nearest 0.1 cm using a Harpenden stadiometer (Holtain Ltd, Crosswell, UK) and expressed as standard deviation scores (height *z*-scores). Neyzi's growth and development charts for Turkish children were used for the evaluation of height (26,27). Standard deviation scores were calculated using the data for Turkish children (28,29).

Standardized insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels were calculated according to values for the population of Turkish children (29). Blood samples were obtained between 8:00 and 8:30 h after an overnight fast for analysis of serum ghrelin, insulin-like growth factor-1, and insulin-like growth factor-binding protein-3 levels.

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Biochemical Assays

Serum concentrations of monohydroxycarbamazepine (the active metabolite of oxcarbazepine) were measured using high-performance liquid chromatography. Serum concentrations of valproate were measured using the fluorescence polarization method with an AxSym analyzer (Abbott Diagnostic Division, Irving, TX, USA). Serum ghrelin levels were measured using a commercial radioimmunoassay kit (Ghrelin human radioimmunoassay kit; Phoenix Pharmaceuticals, Belmont, CA, USA) and samples for quality control were also available with each assay kit. The intra-assay variation was $< 5\%$, and inter-assay variation was $< 14\%$ for the ghrelin kit. Serum insulin-like growth factor-1 concentration was measured by immunoradiometric assay after acid-ethanol extraction (Diagnostics Systems Laboratories, Webster, TX, USA), and the standards were calibrated against the International Reference Preparation 87/518. The detection limit was 0.47 nmol/L (3.6 μg/L), and the intra- and inter-assay coefficients of variation were $< 5.3\%$ for a dose of 8.32 nmol/L (64 μg/L) and $< 5.4\%$ for a dose of 20.41 nmol/L (157 μg/L). Serum insulin-like growth factor-binding protein-3 concentration was measured by immunoradiometric assay (Diagnostics Systems Laboratories), and the standards were calibrated against recombinant insulin-like growth factor-binding protein-3 (mn 28.75 kDa) expressed in *Escherichia coli* obtained from Celtrix Pharmaceuticals (Palo Alto, CA, USA). The

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detection limit was 0.06 nmol/L (1.8 μg/L), and the intra- and inter-assay coefficients of variation were < 5% for a dose of 0.21 nmol/L (6.1 μg/L) and < 10.5% for a dose of 0.74 nmol/L (21 μg/L).

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (version 12.0; SPSS, Chicago, IL, USA). The Shapiro–Wilk test was used to determine whether the variables were normally distributed. Data are presented as mean ± standard deviation or median (25th–75th percentiles), where appropriate. For normally distributed data, one-way repeated-measures analysis of variance was used to test the significant differences between the study groups. For nonnormally distributed data, the Friedman test was used to determine significant differences between the study groups. Either the Bonferroni-adjusted multiple comparison test or the Wilcoxon signed-rank test was employed as the post hoc test, where appropriate. The degree of association between continuous variables was calculated using Pearson's correlation coefficient. A value of $p < 0.05$ was considered statistically significant.

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RESULTS

In total 36 boys and 40 girls with a mean age of 9.1 ± 4.2 years (range, 2 years, 8 months to 16 years, 7 months) were evaluated. Sixty-one percent of patients receiving oxcarbazepine therapy and 55% of patients receiving valproate therapy were prepubertal. The mean age of the 22 prepubertal patients receiving oxcarbazepine therapy was 5.3 ± 1.4 years, while that of the 22 prepubertal patients receiving valproate therapy was 6.6 ± 1.8. The mean age of the 14 pubertal patients receiving oxcarbazepine therapy was 12.6 ± 2.4, while that of the 18 pubertal patients receiving valproate therapy was 14.3 ± 1.3. All patients receiving oxcarbazepine therapy and 60% of patients receiving valproate therapy had partial epilepsy. Plasma drug concentrations in patients receiving oxcarbazepine therapy and in those receiving valproate therapies were similar at the third month (22.2 ± 7.1 vs. 79.7 ± 21.9, respectively) and at the 18th month of therapy (27.0 ± 6.2 vs. 77.0 ± 23.7, respectively).

Standard Deviation Score of Height (Height *z*-score)

In prepubertal patients receiving oxcarbazepine therapy, height *z*-scores were significantly elevated, compared with baseline, at both the 6th and 18th months of oxcarbazepine therapy ($p = 0.008$ and $p = 0.001$, respectively). In pubertal patients receiving oxcarbazepine therapy, height *z*-scores were significantly elevated, compared with baseline, at the 18th month of oxcarbazepine therapy ($p = 0.004$). On the other hand, for prepubertal and pubertal patients receiving valproate therapy, height *z*-scores remained unchanged throughout the study period ($p > 0.05$; Table 1).

Standard Deviation Score of Weight (Weight *z*-Score)

In prepubertal and pubertal patients receiving valproate therapy, weight *z*-scores were significantly elevated, compared with baseline, at both the 6th and 18th months of valproate therapy ($p = 0.001$ and $p = 0.001$; $p = 0.01$ and $p = 0.001$; respectively). On the other hand, for prepubertal and pubertal patients receiving oxcarbazepine therapy, weight *z*-scores remained unchanged throughout the study period ($p > 0.05$; Table 2).

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TABLE 1 Standard Deviation Scores of Height (Height z-Scores) of Prepubertal and Pubertal Patients at the 6th and 18th Months of Valproate and Oxcarbazepine Therapy

	Oxcarbazepine		Valproate	
	Prepubertal patients ($n = 22$)	Pubertal patients ($n = 14$)	Prepubertal patients ($n = 22$)	Pubertal patients ($n = 18$)
Baseline	0.20 (−0.40 to 1.09)	−0.16 (−0.51 to 0.50)	0.17 (−0.57 to 0.50)	0.08 (−0.71 to 0.25)
Month 6	0.33* (−0.40 to 1.16)	−0.17 (−0.47 to 0.50)	0.18 (−0.20 to 0.57)	0.00 (−0.62 to 0.30)
Month 18	0.4** (−0.27 to 1.22)	−0.09* (−0.44 to 0.48)	0.15 (0.00 to 0.45)	0.05 (−0.72 to 0.28)
p-Value	0.001	0.003	0.065	0.219

Data are presented as median values (25th – 75th Percentiles); p-values are obtained via Friedman test.
*$p < 0.01$ as compared with baseline, **$p < 0.001$ as compared with baseline.

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TABLE 2 Standard Deviation Scores of Weight (Weight z-Scores) of Prepubertal and Pubertal Patients at the 6th and 18th Months of Valproate and Oxcarbazepine Therapy

	Oxcarbazepine		Valproate	
	Prepubertal patients ($n = 22$)	Pubertal Patients ($n = 14$)	Prepubertal Patients ($n = 22$)	Pubertal Patients ($n = 18$)
Baseline	0.22 (−0.27 to 0.65)	0.42 (−0.11 to 0.81)	0.30 (−0.43 to 0.86)	0.39 (−.033 to 1.05)
Month 6	0.31 (−0.20 to 1.03)	0.42 (−0.22 to 0.92)	0.63 (−0.23 to 1.13)**	0.73 (0.14 − 1.25)*
Month 18	0.37 (−0.16 to 1.16)	0.49 (−0.23 to 1.10)	0.91 (0.22 to 1.52)**	0.99 (0.29 − 1.57)**
p-Value	0.369	0.131	0.001	0.002

Data are presented as median values (25th–75th Percentiles); p-values are obtained via Friedman test.
*$p < 0.01$ as compared with baseline; **$p < 0.001$ as compared with baseline.

Serum Ghrelin, Insulin-Like Growth Factor-1, and Insulin-Like Growth Factor-Binding Protein-3 Levels

In prepubertal and pubertal patients receiving oxcarbazepine therapy, mean serum ghrelin levels remained unchanged throughout the study period ($p > 0.05$). There were also no significant differences in serum ghrelin levels in prepubertal patients receiving valproate therapy, compared with baseline, at the 6th and 18th months of therapy ($p > 0.05$). On the other hand, in pubertal patients receiving valproate therapy, there was a significant decrease in serum ghrelin levels at the 18th month of therapy, again compared with baseline ($p = 0.006$; Table 3).

In prepubertal patients receiving oxcarbazepine therapy, there was a significant increase in standardized insulin-like growth factor-1 levels at the 18th month of therapy, compared with baseline ($p = 0.011$). However, standardized insulin-like growth factor-1 levels remained unchanged throughout the study period in pubertal patients receiving oxcarbazepine therapy ($p < 0.05$). Although not statistically significant, there was a slight decrease in standardized insulin-like growth factor-1 levels in prepubertal and pubertal patients receiving valproate therapy ($p > 0.05$; Table 4).

In prepubertal patients receiving oxcarbazepine therapy, standardized serum insulin-like growth factor-binding protein-3 levels were significantly increased by the 18th month of therapy compared with baseline ($p = 0.003$). In pubertal patients receiving oxcarbazepine therapy, however, standardized insulin-like growth factor-binding protein-3 levels remained unchanged throughout the study period ($p < 0.05$). In patients receiving valproate therapy, standardized serum insulin-like growth factor-binding protein-3 levels remained unchanged throughout the study period ($p < 0.05$; Table 5).

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TABLE 3 Serum Ghrelin Levels (pg/mL) in Prepubertal and Pubertal Patients Treated with Oxcarbazepine or Valproate

	Oxcarbazepine		Valproate	
	Prepubertal patients ($n = 22$)	Pubertal patients ($n = 14$)	Prepubertal patients ($n = 22$)	Pubertal patients ($n = 18$)
Baseline	291.6 ± 72.79	310.1 ± 59.10	308.63 ± 52.04	333.58 ± 62.65
Month 6	313.6 ± 80.28	287.9 ± 101.70	290.75 ± 61.50	274.71 ± 83.35
Month 18	316.1 ± 84.60	345.1 ± 65.09	282.31 ± 86.36	$245.27 \pm 60.58^*$
p-Value	0.667	0.086	0.066	0.005

Data are presented as mean $\pm$ SD; p-values are obtained via analysis by repeated measures analysis of variance.

$^*p < 0.01$ as compared with baseline.

TABLE 4 Standardized Insulin-Like Growth Factor-1 Levels in Prepubertal and Pubertal Patients Treated with Oxcarbazepine or Valproate

	Oxcarbazepine		Valproate	
	Prepubertal patients ($n = 22$)	Pubertal patients ($n = 14$)	Prepubertal patients ($n = 22$)	Pubertal patients ($n = 18$)
Baseline	0.20 (−0.43 to 1.03)	0.45 (−0.49 to 0.75)	−0.20 (−0.62 to 0.50)	−0.40 (−0.50 to −0.10)
Month 6	0.60 (−0.20 to 1.40)	0.60 (−0.44 to 0.90)	−0.30 (−1.60 to 0.83)	−0.10 (−0.50 to 0.15)
Month 18	0.76* (−0.11 to 1.41)	0.76 (−0.46 to 1.25)	−0.30 (−0.70 to 0.20)	−0.20 (−0.60 to 0.15)
p-Value	0.012	0.157	0.415	0.729

Data are presented as median values (25th–75th Percentiles); p-values are obtained via Friedman test.

$^*p < 0.05$ as Compared with Baseline.

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TABLE 5 Standardized IGFBP-3 Levels in Prepubertal and Pubertal Patients Treated with Oxcarbazepine or Valproate

	Oxcarbazepine		Valproate	
	Prepubertal patients ($n = 22$)	Pubertal patients ($n = 14$)	Prepubertal patients ($n = 22$)	Pubertal patients ($n = 18$)
Baseline	0.05 (−0.85 to 1.02)	0.05 (−0.33 to 0.60)	0.10 (−0.72 to 0.50)	−0.20 (−0.50 to 0.81)
Month 6	0.40 (−0.88 to 0.89)	0.53 (−0.33 to 0.95)	0.50 (0.10 to 0.65)	0.10 (−0.75 to 0.50)
Month 18	0.43* (−0.73 to 0.71)	0.55 (−0.38 to 0.93)	0.50 (−0.15 to 0.60)	0.10 (−0.60 to 0.65)
p-Value	0.012	0.616	0.872	0.967

Abbreviation: IGFBP-3, insulin-like growth binding protein-3.
Data are presented as median values (25th–75th Percentiles); *p*-values are obtained via Friedman test.
*$p < 0.01$ as compared with baseline.

TABLE 6 The Correlation of Serum Ghrelin Levels with Serum IGF-1 and IGFBP-3 Levels in Prepubertal and Pubertal Children with Epilepsy During Monotherapy with Valproate

	Prepubertal		Pubertal	
	IGF-1	IGFBP-3	IGF-1	IGFBP-3
Month 3	r = 0.503	$r = 0.310$	$r = 0.448$	$r = 0.262$
	$p = 0.117$	$p = 0.161$	$p = 0.068$	$p = 0.294$
Month 6	$r = -0.018$	$r = -0.014$	$r = -0.613$	$r = 0.356$
	$p = 0.938$	$p = 0.952$	$p = 0.109$	$p = 0.161$
Month 18	$r = -0.222$	$r = -0.237$	$r = -0.391$	$r = 0.011$
	$p = 0.347$	$p = 0.315$	$p = 0.108$	$p = 0.965$

Abbreviation: IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth binding protein-3.

TABLE 7 The Correlation of Serum Ghrelin Levels with Serum IGF-1 and IGFBP-3 Levels in Prepubertal and Pubertal Children with Epilepsy During Monotherapy with Oxcarbazepine

	Prepubertal		Pubertal	
	IGF-1	IGFBP-3	IGF-1	IGFBP-3
Month 3	$r = -0.017$	$r = -0.227$	$r = 0.284$	$r = 0.027$
	$p = 0.941$	$p = 0.309$	$p = 0.324$	$p = 0.927$
Month 6	$r = 0.434$	$r = 0.314$	$r = -0.078$	$r = 0.337$
	$p = 0.064$	$p = 0.190$	p =0.792	$p = 0.238$
Month 18	$r = 0.313$	$r = 0.401$	$r = 0.106$	$r = -0.137$
	$p = 0.179$	$p = 0.080$	$p = 0.719$	$p = 0.941$

Abbreviation: IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth binding protein-3.

There was no significant correlation between serum ghrelin levels and serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels in prepubertal and pubertal patients receiving valproate and oxcarbazepine therapies (Tables 6 and 7).

There was no significant correlation between weight and serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels in prepubertal and pubertal patients receiving valproate and oxcarbazepine therapies. There was a negative correlation between weight gain and ghrelin in the subjects using Valproic acid (VPA) in both prepubertal (6th month; $r = 0.503$, $p = 0.017$) and pubertal cases (3rd and 6th months; $r = -0.512$, $p = 0.024$ and $r = -0.613$, $p = 0.009$, respectively) (data not shown). There were no gender differences in hormonal or auxological changes during treatments (data not shown).

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DISCUSSION

This prospective study of idiopathic epilepsy patients showed that valproate therapy had no effect on linear growth, while oxcarbazepine stimulated linear growth by increasing serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels. On the other hand, oxcarbazepine had no effect on serum ghrelin levels, while serum ghrelin levels were decreased with valproate therapy. There was no significant correlation between increased insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels and ghrelin level in oxcarbazepine-treated patients.

Although there have been few studies reporting negative effects of valproate therapy on linear growth (15,16), in agreement with the findings of Kumandaş et al. (11) and Mikkonen et al. (14), we determined normal serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels, as well as normal linear growth in children with idiopathic epilepsy treated with valproate monotherapy. In a previous study, Coiro et al. (30) reported that short-term exposure to valproate stimulated growth hormone release. This finding has not been corroborated by further studies. Recently, El-Khayat et al. (12) reported that treatment with valproate did not affect growth hormone levels in children and in fact inhibited the expected increase in post-provocation of growth hormone and insulin-like growth factor-1 levels. Similarly, Rattya et al. (10) suggested that endogenous growth hormone secretion did not increase during long-term valproate treatment, because linear growth was not accelerated and serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels remained normal. Furthermore, Isojarvi et al. (7) noted normal levels of insulin-like growth factor-1 in women receiving valproate for epilepsy. In accordance with these previous findings, endogenous growth hormone did not seem to be elevated in patients undergoing valproate therapy in this study; linear growth was not accelerated, nor were insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels significantly changed throughout the study period.

Mikkonen et al. (14) reported that treatment with oxcarbazepine had no remarkable effects on linear growth and final height in children. However, they did not investigate serum growth hormone, insulin-like growth factor-1, and insulin-like growth factor-binding protein-3 levels in their study. It has been shown that oxcarbazepine treatment is not associated with altered serum insulin-like growth factor-binding protein-3 concentrations in children (10,11). In contrast to these data regarding insulin-like growth factor-binding protein-3 levels, Rattya et al. (10) demonstrated high plasma insulin-like growth factor-1 levels in girls receiving oxcarbazepine for epilepsy. However, they reported that increased plasma insulin-like growth factor-1 levels did not lead to accelerated growth (10). In that particular study, the girls who were treated with oxcarbazepine during the prepubertal period were shorter than the healthy control girls at baseline; however, their final height was normal at follow-up examinations after the initiation of oxcarbazepine therapy. It may be that high plasma insulin-like growth factor-1 levels in these girls, who were shorter than the healthy control girls at baseline, increased linear growth, so that final height in these girls was similar to that of healthy controls by the end of the study. In our study, we noted a significant increase in circulating insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels during oxcarbazepine therapy. We also found that increases in insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels were parallel to acceleration in growth in prepubertal patients. These findings raise the possibility that oxcarbazepine induces linear growth. However, it is difficult to draw a definitive conclusion regarding whether

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there was a change in final height, since the study period was quite limited considering the long period of growth, and growth rates in children can vary during different time periods. Moreover, we did not determine the circulating growth hormone levels of the study population; we cannot, therefore, suggest that increases in height and in serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels are correlated with an increase in growth hormone level. On the other hand, it may be that oxcarbazepine stimulates insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 production in the liver by inducing liver enzymes (10), leading to altered serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 profiles, similar to the altered thyroid hormone profile induced by antiepileptic drugs (3).

Ghrelin is one of the factors stimulating growth hormone secretion. To the best of our knowledge, there have been no previous studies of the correlation between total ghrelin level and growth or insulin-like growth factor-1 and insulin-like growth factor-1 in either pubertal or prepubertal children using antiepileptics. The very few studies reporting a correlation between ghrelin and growth or insulin-like growth factor-1 have shown either a negative correlation or no correlation at all (31,32). Muller et al. (33) reported positive correlations between ghrelin, growth hormone, and insulin-like growth factor-1 levels in healthy, nonobese volunteers, suggesting that ghrelin is associated with linear growth via the growth hormone, insulin-like growth factor-1 axis. In contrast to this conclusion, our findings revealed no change in the serum ghrelin levels of oxcarbazepine-treated patients (both prepubertal and pubertal patients), whereas there were significant increases in serum concentrations of insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 in prepubertal patients. Additionally, serum ghrelin levels were decreased throughout the study period in pubertal patients receiving valproate therapy, but there was no significant correlation between these decreased serum ghrelin levels and serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels. The findings of the current study may therefore indicate that ghrelin does not induce linear growth, nor does it appear to modulate circulating levels of insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 in either valproate- or oxcarbazepine-treated epileptic patients. However, it must not be forgotten that the absence of a correlation between serum ghrelin levels and serum insulin-like growth factor-1 and insulin-like growth factor-1 may also be due to the methodological analysis (wide dispersion and need for a greater sample size). For that reason, prospective studies with a greater sampling volume and a control group are needed in order to reveal this correlation. As well as being a powerful growth hormone release inducer, ghrelin exhibits orexigenic activity being involved in the regulation of appetite and energy balance (31–35). VPA-related obesity has reported to be common in both children and adult epileptic patients (36–38). In accordance with findings of the current study, we have also shown in recent studies that VPA, but not OXC, causes weight gain in children (21,36). We have also shown a correlation between increased weight gain and decreased ghrelin levels in children using VPA, in both the current study and our previous paper (36). Cummings et al. (39) also showed that elevated VPA-associated weight gain is correlated with increased energy balance and decreased ghrelin levels. Under the lights of the available findings, it can be concluded that ghrelin may not be directly associated with VPA-induced weight gain, and serum levels may decline as a response to weight gain (36,39).

The main limitation of the current study was the lack of a control group. The presence of an age- and gender-matched control group might have strengthened the study. This limitation was mitigated by the prospective design of the study (the baseline values served as control values).

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In conclusion, exposure to oxcarbazepine, but not to valproate, during prepubertal and pubertal periods, may affect linear growth, possibly via mechanisms involving increases in insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels. Considering the importance of these findings in terms of linear growth during childhood, long-term follow-up studies are warranted to further investigate the relationship between oxcarbazepine and linear growth.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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