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Evaluation of the Detrimental Effects of some Antiepileptic Drugs on the Height and Weight of Children with Epilepsy

Abdullah Shakir Mahmood[*], Aseel S. Al Mallakhdeer[*] , Muhammad A. Alkataan[*,1] and Mahfoodh S. Hasan[*]

[*] College of Medicine, Ninevah University ,Ninevahm, Iraq

Abstract

Growth is a multifactorial process influenced by genetic, nutritional, hormonal, psychosocial and other factors including the general health of a child. Epilepsy is defined as a chronic condition characterized by recurrent clinical events or epileptic seizures, which occur in the absence of a metabolic or toxic disease the drugs that are used in the treatment of this condition can affect patients' growth due to their mechanisms of action. This study aimed to evaluate the effect of some antiepileptic drugs on growth (height and weight) in children with epilepsy. This work involved 51 newly diagnosed children with a different form of epilepsy (Generalized, absent and partial). Patients were collected from the outpatient's clinic in Al Salam teaching hospital and private clinic in Mosul city from July 2018 to July 2020. Patients were divided into three groups of 17 patients each according to the treatment (group one patients on Carbamazepine monotherapy with dose mean 13.3 ± 4.8 mg/Kg, group two patients on Valproic acid monotherapy with a dose of 14.4± 3.3 mg/kg and the last group involve patient on combined therapy Carbamazepine 10.8±5.8mg/Kg plus 19.7± 8.8 mg/Kg of Valproic acid. Patients ages range from 5-11 years, with an Initial BMI range of 12-20. The results of this work showed that Carbamazepine monotherapy caused no significant effect on both BMI values after 6 and 12 months of treatment. Valproic acid monotherapy significantly elevated BMI after 6 and 12 months of treatment. Combined therapy showed no significant effect on BMI. The patient's centile height significantly elevated after 6 and 12 months of Valproic acid compared to the normal growth according to the growth chart. While both Carbamazepine and combined therapy showed no significant change in comparison with the normal growth according to the growth chart. In conclusion, children with epilepsy who use antiepileptic drugs need a restricted monitor policy for their growth, especially those on Valproic acid.

Keywords: Growth, weight, percentile, Carbamazepine, Valproic acid.

تأثير الأدوية المضادة للصرع على بعض متغيرات النمو لدى الأطفال المصابين بأنواع مختلفة من الصرع

عبد الله شاكر محمود [*]، اسيل سامي الملا خضر [*] محمد عبد الغفور القطان[*،1] و محفوظ سليمان حسن[*]

[*] كلية الطب، جامعة نينوى، نينوى، العراق.

الخلاصة

ان النمو عملية معقدة تتأثر بالعوامل الوراثية والتغذوية والهرمونية والنفسية والاجتماعية وعوامل أخرى بما في ذلك الصحة العامة للطفل. يُعرَّف الصرع بأنه حالة مزمنة تتميز بأعراض سريرية متكررة أو نوبات صرع، والتي تحدث في حالة عدم وجود مرض استقلابي أو سام، يمكن للأدوية التي تستخدم في علاج هذه الحالة أن تؤثر على نمو المرضى بسبب آليات عملها. هدفت هذه الدراسة إلى تقييم تأثير بعض الأدوية المضادة للصرع على النمو (الطول والوزن) لدى الأطفال المصابين بالصرع. شمل هذا العمل ٥١ طفلًا تم تشخيصهم حديثًا بنوع مختلف من الصرع (معمم وغائب وجزئي). تم تقسيم المرضى إلى ثلاث مجموعات وفقًا للعلاج (المجموعة الأولى من المرضى الذين عولجوا بكاربامازيبين وحيدًا بجرعة متوسط ١٣,٣ ± ٤,٨ مجم / كجم، مجموعة مريضين في العلاج الأحادي لحمض الفالبرويك بجرعة ١٤,٤ ± ٣,٣ مجم / كجم والمجموعة الأخيرة تشمل المريض على العلاج المركب Carbamazepine 10.8 ± 5.8 بالإضافة إلى ١٩,٧ ± ٨,٨ من حمض الفالبرويك. تتراوح أعمار المرضى بين ١١- سنة، مع نطاق أولي لمؤشر كتلة الجسم من ١٢-٢٠. وأظهرت نتائج هذا العمل أن العلاج الأحادي بالكاربامازيبين لم يكن له تأثير كبير على قيم مؤشر كتلة الجسم. بعد ٦ و١٢ شهرًا من العلاج. أدى العلاج الأحادي بحمض الفالبرويك إلى رفع مؤشر كتلة الجسم بشكل ملحوظ بعد ٦ و١٢ شهرًا من العلاج. لم يظهر العلاج المشترك أي تأثير كبير على مؤشر كتلة الجسم. ارتفع الارتفاع المئوي للمريض بشكل ملحوظ بعد ٦ و١٢ شهرًا٥١ من استخدام حمض الفالبرويك مقارنة بالنمو الطبيعي وفقا لجدول النمو، بينما لم يظهر كل من العلاج بالكاربامازيبين والعلاج المركب أي تغيير معنوي مقارنة بالنمو الطبيعي وفقًا لمخطط النمو. أيون، يحتاج الأطفال المصابون بالصرع الذين يستخدمون الأدوية المضادة للصرع إلى سياسة مراقبة مقيدة لنموهم، وخاصة أولئك الذين يتناولون حمض الفالبرويك.

الكلمات المفتاحية: النمو، الوزن، النسبة المئوية، كاربامازيبين، حمض الفالبرويك.

[1]Corresponding author E-mail: moh1977729@gmail.com
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Introduction

Growth is a multifactorial process influenced by genetic, nutritional, hormonal, psychosocial and other factors including the general health of a child [1]. Deviation from a normal pattern of growth can be the first manifestation of a wide variety of disease processes, including endocrine and non-endocrine disorders and may involve virtually any organ system of the body [2]. The rate of linear growth and the physiologic components regulating it varies with age [3]. The proliferation of epiphyseal growth plate results from complex interactions between hormones and growth factors, which may directly or indirectly affect the serum levels of calcium and the condition of those cells, leading to final stature [4]. The most powerful tool in growth assessment is the growth chart used in combination with accurate measurements of height, weight, head circumference, and calculation of the body mass index [5].

The growth trajectory of each stage of growth (fetal, infant (I), childhood (C) and pubertal (P)) can be represented mathematically by the 'ICP growth model'. Growth during the first 3 years results from a combination of a rapidly decelerating infancy component and a slowly decelerating childhood component. The latter dominates the mid-childhood years but it is altered by the pubertal contribution, which is modelled on a sigmoid curve [2]. Epilepsy is defined as a chronic condition characterized by recurrent clinical events or epileptic seizures, which occur in the absence of a metabolic or toxic disease or fever [6,7].

The International League against Epilepsy recognizes two major categories of epileptic seizures, based on clinical and electroencephalographic (EEG) features: focal seizures and generalized seizures. Focal seizures originate within neural networks involving one hemisphere of the brain and more or less localized at the onset, whereas generalized seizures start in and rapidly involve networks in both cerebral hemispheres [6]. Among partial seizures, those in which awareness is impaired are termed complex, whereas those in which awareness is preserved are termed simple [8].

For infants and children with their first unprovoked seizure, urgent laboratory studies with neuroimaging should be considered, depending on the history and physical findings. The definitive neuro-diagnostic evaluation, consisting of an EEG and neuroimaging study, of pediatric patients with seizures typically performed on an outpatient basis. The EEG could help in the assessment of the child with a first seizure, especially if an epileptic syndrome is identified; however, a normal EEG does not rule out seizures. Although an EEG when performed within 24 hours of the fit, if abnormalities were found, these abnormalities may be due to the postictal condition. Typically, the EEG is performed on an outpatient basis within 2 weeks of the first seizure [7, 9].

The Age and seizure type of the patient are two important factors that should be considered in choosing an anticonvulsant. For generalized tonic-clonic or focal onset seizures in infants up to 6 months of age, phenobarbital is often chosen first, given its ease of use, predictable blood levels and modest side-effect profile. For older infants or children with focal onset seizures, oxcarbazepine or levetiracetam is the preferred medication. Levetiracetam is commonly used for generalized tonic-clonic seizures at any age [10].

Divalproex (valproate, divalproex sodium) is a broad-spectrum AED that can be used in all types of generalized epilepsy, including absence, primary GTCS and myoclonic; Absence seizures can be treated with ethosuximide, and then when GTCS seizures appear, Divalproex or lamotrigine can be used, because ethosuximide does not cover other types than absence. Practitioners should monitor the efficacy and side-effects of anticonvulsant therapy, help in dose adjustment of anticonvulsants in patients – especially those receiving single anticonvulsants – and reviewing seizure precautions frequently to encourage healthy and safe living [9,11].

Discontinuation of AEDs can be scheduled when the child is seizure-free for at least 2 years AED therapy should be discontinued gradually; over at least 3-6 months, sudden discontinuation can lead to withdrawal seizures or status epilepticus [1,2]. This study aimed to evaluate the effect of some antiepileptic drugs on growth (height and weight) in children with epilepsy. As mentioned above, that antiepileptic agents can affect the proliferation of epiphyseal growth plate, affecting the serum levels of calcium leading to short stature [4]. This work will assess growth according to the growth chart.

Material and Methods

This work involved 51 newly diagnosed children with different forms of epilepsy (Generalized, absent and partial). Patients were collected from the outpatient's clinic in Al-Salam teaching hospital and private clinic from July 2018 to July 2020. Patients were divided into three groups according to the treatment (group one includes 17 patients on Carbamazepine monotherapy with a dose mean of 13.3 ± 4.8 mg/Kg. Group two include 17 patients on Valproic acid monotherapy with a dose of 14.4± 3.3 mg/kg, and the last group involve 17 patients on combined therapy Carbamazepine 10.8±5.8 mg/ Kg plus 19.7± 8.8 mg /Kg of Valproic acid. The patient`s ages ranged from 5-11 years, with an initial BMI range of 12-20. Patients have good physical activity with no other CNS disorders. Patients with any other health problems were excluded from this work. Height was measured using standard Human Balance RGT.B-200-RT

(Clover-surgical- Germany). BMI was calculated using the following equation: BMI = kg/m^2.

CDC Chart was used as the standard for comparison to patients reading[5]. BMI measurement of the patient's monitors for one year as patients showed no problems with their medication (baseline, 6 months, and 12 months). Exclusions were maternal smoking, gestational age outside the normal range, and residence outside the study area. Refuse to participate in the study. Other exclusions, including an inability to contact family and children who have travelled outside of the area or mental retardation, and cerebral palsy [12].

Data were presented as Mean ±Standard deviation. ANOVA used to analyze the data. Change with $p<0.05$ is considered to be statistically significant. Excel 2010 software was used in the analysis.

Results

The patient's centile weight significantly elevated after 6 and 12 months of Valproic acid ($p<0.01$) compared to the normal growth according to the CDC growth chart. While both Carbamazepine and combined therapy showed no significant change in comparison with the normal growth according to the growth chart ($p>0.05$).

The results of this work showed (Table 1 and Table 2) that Carbamazepine monotherapy caused no significant effect on both BMI values after 6 and 12 months of treatment ($p>0.05$). Valproic acid monotherapy significantly elevated BMI after 6 and 12 months of treatment ($p>0.01$). Combined therapy showed no significant effect on BMI. No significant effect on waist circumference was noticed when compare Valproic acid and combined therapy protocols to Carbamazepine protocol.

Table 1. BMI of children after treatment with Carbamazepine, Valproic acid and combined therapy.

Parameter	Baseline Mean ± SD	Six months Mean ± SD	Twelvemonths Mean ± SD	*P-Value*
Carbamazepine (Patient No. =17)	15.9± 3.7	16.92±3.72	19.14±3.7	*0.54*
Valproic acid (Patient No. =17)	17±4	18.95±2.69	21.12± 1.84	***0.01****
Combined therapy (Patient No. =17)	15.78±1.56	16.88±2.78	19.59± 3.25	0.61

* Represent significant change ($p<0.05$).

Table 2. Waist circumference of children after treatment with Carbamazepine, Valproic acid and combined therapy.

Parameter	Baseline Mean ± SD	Six months Mean ± SD	Twelvemonths Mean ± SD
Carbamazepine (Patient No. =17)	47.1± 6.3	51.52±17	54.4±6.5
Valproic acid (Patient No. =17)	48.54±9	52.87±10	54.93± 5.13
Combined therapy (Patient No. =17)	47.05±4.35	52.48±9.75	54.65± 9.07

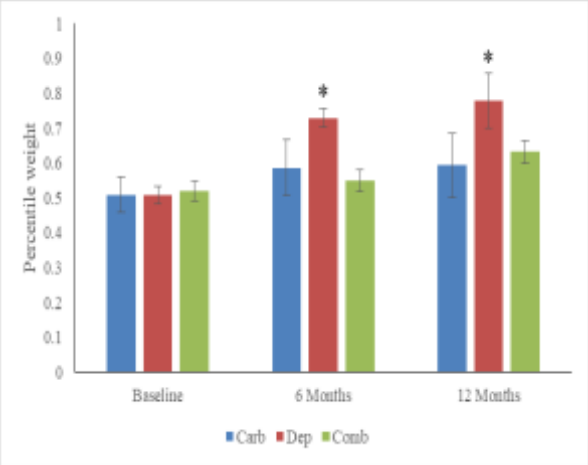

Figure 1. Percentile weight of patients after 6 and 12 months of treatment.

The patient's centile height significantly elevated after 6 and 12 months of Valproic acid ($p<0.01$) compared to the normal growth according to the growth chart. While both Carbamazepine and combined therapy showed no significant change in comparison with the normal growth according to the growth chart ($p>0.05$).

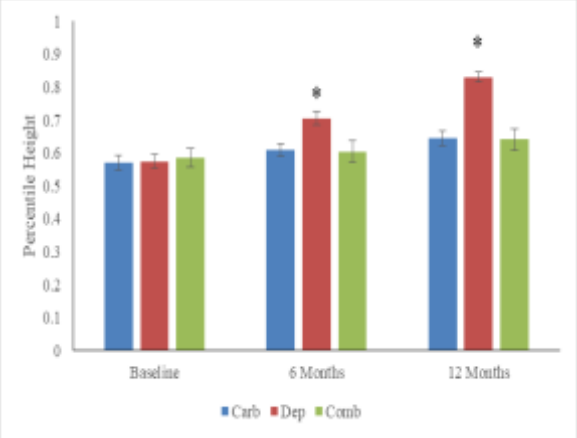

Figure 2. Percentile Height of patients after 6 and 12 months of treatment

Discussion

This study was conducted to explain the effect of antiepileptic on some growth profile parameters after 6 and 12 months of treatments. Carbamazepine had no significant influence on growth, centile-weight, or centile-height. This might be due to the drug's mini effect on resting metabolic rate, as reported by Herman et al., [11]; however, this does not go with Inaloo et al., 2020 [12].

In contrast, Valproic acid significantly increases the BMI of epileptic patients by increasing body fat due to the elevation of their serum triglycerides and this agrees with Inaloo et al, 2020 [13]. Combined therapy showed no significant effect on BMI and this may be related to significant induction of many cytochromes metabolism and clearance which lead to these effects and this agree with Saruwatari et al 2010 [14].

Valproic acid showed significant elevation in BMI, percentile height and weight after 6 months of therapy and this disagrees with results obtained by lee and his group who described that Valproic acid significantly reduced pediatric patient's Longitudinal growth. Lee et al., 2013 and might be due to the effect of Valproic acid to inhibit proliferation of growing plate chondrocytes but not changing serum calcium. In patients on Carbamazepine and combined therapy, the result of this work agree with Lee results as he uses oxcarbazepine showed no significant effect on in stature growth of patients [15].

The impacts of epilepsy on bone, drugs used to treat epilepsy increased the possibility of bone fracture by different mechanisms. The fracture rate in patients on anti-epileptic drugs is 2–6 times higher than the normal population. This increment in break chance in subjects with epilepsy is comparable to that seen with incessant steroid use as this drugs affects bone mass by affecting bone remodeling factors [16].

In conclusion, children with epilepsy who use antiepileptic drugs need a restricted monitor policy for their growth, especially those on Valproic acid.

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