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ORIGINAL ARTICLE

Omega-6/omega-3 ratio and cognition in children with epilepsy☆

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Received 22 May 2018; accepted 24 July 2018
Available online 26 February 2019

KEYWORDS
Omega-3;
Omega-6;
Cognition;
Idiopathic epilepsy;
Children

Abstract
Introduction: Cognitive impairment is a common consequence of epilepsy in children. This study aimed to assess the ratio of omega-6 to omega-3 fatty acid levels and its impact on cognitive function in children with idiopathic epilepsy.
Patients and methods: We performed a case-control study in 30 children with idiopathic epilepsy and 20 healthy children. We measured levels of alpha-linolenic acid (omega-3) and linoleic acid (omega-6) by means of gas-liquid chromatography. We assessed cognitive function with the Arabic version of the fourth edition of the Stanford-Binet test and the P300 component of event-related potentials. All children had an intelligent quotient greater than 70.
Results: Children with epilepsy had lower levels of omega-3 and higher levels of omega-6 fatty acids and an abnormal omega-6/omega-3 ratio compared to non-epileptic children. We found a significant positive correlation of serum omega-3 levels and a significant negative correlation of serum omega-6 levels with cognitive function scores and P300 latency in children with epilepsy.
Conclusion: Children with epilepsy have abnormal ratios of omega-6 to omega-3 fatty acid serum levels, which is associated with impaired cognitive function in these children.

☆ Please cite this article as: Bahgat KA, Elhady M, Abdel Aziz A, Youness ER, Zakzok E. Cociente omega-6/omega-3 y cognición en niños con epilepsia. An Pediatr (Barc). 2019;91:88–95.

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PALABRAS CLAVE
Omega-3;
Omega-6;
Cognición;
Epilepsia idiopática;
Infancia

Cociente omega-6/omega-3 y cognición en niños con epilepsia

Resumen
Introducción: El deterioro cognitivo es una consecuencia común de la epilepsia en niños. El objetivo del estudio fue evaluar el cociente de los niveles de ácidos grasos omega-6 y omega-3 y su impacto en el funcionamiento cognitivo de niños con epilepsia idiopática.
Pacientes y métodos: Estudio de casos y controles en 30 niños con epilepsia idiopática y 20 niños sanos. Se midieron los niveles plasmáticos de ácido alfa-linolénico (omega-3) y de ácido linoleico (omega-6) mediante cromatografía de gases. El funcionamiento cognitivo se evaluó mediante la versión en árabe de la cuarta edición de la escala de Stanford-Binet y la onda P300 en potenciales relacionados con eventos. Todos los participantes tenían un cociente intelectual superior a 70.
Resultados: Los niños con epilepsia tenían niveles más bajos de omega-3 y más altos de omega 6 y un cociente omega-6/omega-3 anormal en comparación con los niños sanos. Se observó que el nivel plasmático de omega-3 se correlacionaba positivamente y el nivel de omega-6 negativamente, ambos de manera significativa, con las puntuaciones del funcionamiento cognitivo y la latencia de la onda P300 en niños con epilepsia.
Conclusión: Los niños con epilepsia tienen un cociente alterado de los niveles plasmáticos de ácidos grasos omega-6 y omega-3 que se asocia al deterioro cognitivo en este grupo.

Introduction

Epilepsy is a heterogeneous neurological disorder characterized by a constant predisposition for unprovoked seizures.[1] Cognitive impairment is a common consequence of epilepsy in children. It has been reported that 40% of children with epilepsy have cognitive disorders.[2] An ongoing epileptogenic process can produce irreversible neurological damage, especially in the maturing brain and even if seizures are controlled, causing permanent cognitive and intellectual deficits. Despite having an intelligence quotient in the normal range, 25% of children with epilepsy have subtle cognitive impairments that are frequently undiagnosed. Cognitive deficits can lead to significant learning disabilities that have a negative impact on social and educational outcomes. Early identification of modifiable risk factors and proper intervention are necessary in order to prevent cognitive impairment and improve the quality of life of these children.[3]

The effect of nutrition on neurologic function and brain health is an area of great interest, especially as regards omega fatty acids. Nutritional-cognitive research has been growing at a fast pace and the emerging evidence supports that omega-3 supplementation has beneficial effects in many neuropsychiatric disorders. Linoleic acid (Omega-6) and alpha-linolenic acid (omega-3) are essential fatty acids that should be obtained from the diet. They are precursors for arachidonic acid, eicosapentaenoic acid and docosahexaenoic acid, which are important for brain development and function.[4]

Omega-3 fatty acid is critical for neuronal cell membrane integrity, cell differentiation and neurogenesis in the developing brain. Adequate omega-3 fatty acid supplementation is essential for proper neurologic function, including brain plasticity and synaptic transmission.[5] What matters is not only the availability of fatty acids, but also that they are adequately balanced in diet. Optimally, the ratio of omega-6 to omega-3 fatty acids should not exceed 4:1. Most modern diets contain excessive amounts of saturated and omega-6 fatty acids and insufficient amounts of omega-3 fatty acid. There are rising concerns that inadequate intake of omega-3 in the modern diet may have an adverse impact on cognitive function and attention.[6] Experimental animal studies have shown that balanced supplementation of omega-3 and omega-6 fatty acids can effectively enhance learning, raise the pain threshold and improve sleep quality and thermoregulation.[7] Imbalance of these fatty acids in the brain has been linked to several neurological and psychiatric disorders.[8] Therefore, a balanced diet has emerged as a non-invasive and effective approach for the management of neurological and cognitive disorders.[9] However, there are insufficient data regarding the omega-6 to omega-3 ratio and its association with cognitive function in children with epilepsy.

In this study, we assessed the omega-6 to omega-3 fatty acid level ratio and its impact on cognitive function in children with epilepsy.

Patients and methods

We conducted a single centre, cross-sectional comparative study in a group of 30 children with idiopathic epilepsy and a control group of 20 healthy children matched for age and sex. We recruited children with epilepsy from the paediatric neurology clinic and controls from the patients that visited the paediatric outpatient clinic of the Alzahraa University Hospital in Al-Azhar University (Cairo, Egypt) between

December 2014 and January 2016. The study was conducted after obtaining informed consent from the caregivers of participants and the approval of the Ethics Committee of Al-Azhar University.

The inclusion criteria for the case group were a confirmed diagnosis of idiopathic epilepsy and age 5–15 years old. The control group comprised 20 children matched with the epilepsy group for age, sex, educational attainment of parents and patients, nutritional intake and socioeconomic status. All participants had intelligent quotients greater than 70, assessed with the fourth edition of the Stanford-Binet test.

We excluded children with any form of psychiatric, physical, developmental or intellectual disability, chronic underlying disease (e.g. inborn error of metabolism, genetic, endocrine or liver disease, vision or hearing impairment) or neurologic disorders other than epilepsy. We also excluded from the study children with obesity and those that received any drugs or compounded preparations that could affect their fatty acid levels.

We took a detailed medical history of all participants, including the age of onset, the frequency of seizures, antiepileptic medication, school performance, seizure control over the previous year, socioeconomic status, nutritional, developmental, perinatal history, and educational attainment of the patient as well as the parents. The diagnosis of epilepsy was based on the history from reliable eye witness accounts and confirmed by electroencephalography (EEG). We classified patients according to the Commission on Classification and Terminology of the International League against Epilepsy.[10]

The patients underwent full systemic and neurologic evaluations. Psychiatric and hearing assessments were performed to rule out psychiatric morbidity and hearing loss. We measured the intelligence quotient by means of the Arabic version of the fourth edition of the Stanford-Binet test.[11] Children with epilepsy underwent neuroimaging tests to exclude the presence of underlying structural brain lesions.

We evaluated cognitive function using the Arabic version of the Stanford-Binet test, fourth edition, a standardized and validated instrument that assesses four major cognitive skills (verbal reasoning, visual/abstract reasoning, short term memory, quantitative reasoning) through several subscales in addition to measuring the intelligence quotient. The number of subtests administered varies according to the age and ability of the child. In this study, we administered the same core subtests to all children. We used a short form of the test consisting of 6 subtests that assess 4 aspects of cognition, and then calculated the overall score.

We evaluated the P300 wave in event-related potentials (ERPs) in all participating children at the paediatric neurology unit of the Alzahraa University Hospital to assess auditory-based cognitive processing and attention. We explained the task to each child, ensuring that they understood it well and performed the task correctly. To guarantee their complete attention, children were asked to count the number of rare stimuli and compare it with the number reported by the equipment. The P300 wave is the highest positive peak after the N1, P2 and N2 waves, and its latency ranges between 225 and 396 milliseconds. The latency represents the ability to discriminate a rare stimulus appearing among standard stimuli. The P300 amplitude ranges between 5 and 40 microvolts. The amplitude is the distance between the maximum positive value and the maximum negative value of the wave, and varies as a function of the improbability of the stimulus.[12]

Omega fatty acids serum level

Using aseptic technique, we obtained 5 mL samples of venous blood from the patients after an overnight 12-h fast. The samples were centrifuged immediately after collection and the serum stored at $-80\,^{\circ}C$. The serum levels of the main omega fatty acids (alpha-linolenic acid [18:3 omega-3], linoleic acid [18:2 omega-6]) were measured by means of high-performance liquid chromatography (HPLC).

Each standard fatty acid fraction was dissolved in acetonitrile and serial dilutions prepared from which 20 μL were injected in HPLC. The standard curve was drawn for each fraction. For each sample from participants, cell plasma was homogenized in a 2% acetic acid-ethyl ether mixture (2:1 v/v). This solution was filtered and centrifuged at $500 \times g$ and the organic phase dried under a nitrogen gas stream. The resulting residue was then dissolved in 500 μL acetonitrile to be ready for injection in the HPLC system.[13]

The analysis was made in an Agilent 1100 series HPLC system. Fatty acids were separated on a Phenomenex stainless steel and 300–390 mesh silica HPLC column (with 10 μm spherical particles). This process was performed following the method described by Aveldano et al. with some modifications,[14] with a C18 HPLC column (250×4.6, particle size 5 μL), a 70/30 v/v acetonitrile–water mixture mobile phase, isocratic elution at a flow rate of 1 mL/min and an ultraviolet detector set at a wavelength of 200 nm. A 20 μL aliquot of each fraction was injected in the system.

Statistical analysis

We performed the statistical analysis of the data with the Statistical Package for Social Sciences, version 21 (Chicago, IL, USA). We summarized qualitative data as absolute frequencies and percentage and quantitative data as mean and standard deviation. We analyzed differences between groups with the *t* test for independent samples. We assessed the correlation between cognitive scores, serum levels of omega fatty acids and P300 measurements with the Pearson correlation coefficient. We defined statistical significance as a *P*-value of less than .05 in any of the tests.

Results

The study included 30 children with epilepsy (21 male, 9 female) aged 5–15 years. The age at onset of epilepsy ranged from 1 to 10 years (3.54 ± 1.85 years), and the duration of illness from 6 months to 11 years (6.78 ± 2.81 years). When it came to the clinical manifestations and EEG findings, 17 patients (56.7%) had generalized seizures, 2 (6.7%) focal seizures and 3 (10%) focal to bilateral tonic-clonic seizures, while 8 (26.7%) had normal EEG findings. As for pharmacological treatment, 20 (66.7%) received a single antiepileptic drug (carbamazepine, valproic acid or levetiracetam) and 6 (20%) a combination of drugs. Pharmacological treatment

Table 1 Comparison of demographic characteristics, omega fatty acid serum levels and P300 event-related potentials of children with epilepsy and healthy controls.

Variable	Children with epilepsy ($n=30$)	Children without epilepsy ($n=20$)	Independent samples t test	
	Mean ± SD	Mean ± SD	t	P
Demographic characteristics				
Age (years)	10.83 ± 3.87	10.16 ± 4.23	1.824	0.077
Sex (male/female) (n, %)	21 (70%)/9(30%)	9(45%)/11(55%)	3.125	0.074
Socioeconomic status (n, %)				
Middle	20 (66.67%)	11 (555)	0.693	0.405
Low	10 (33.33%)	9 (45%)		
Child level of education (n, %)				
Primary education	12 (40%)	9 (45%)	0.123	0.726
Secondary education	18 (60%)	11 (55%)		
Parental educational attainment (n, %)	5 (16.67%)	3 (15%)	0.025	0.875
High school University degree	25 (83.33)	17 (85%)		
Polyunsaturated fatty acid serum levels				
Omega-3 (μmol/L)	246.98 ± 132.31	324.97 ± 80.93	3.010	0.003*
Omega-6 (μmol/L)	2800.22 ± 1299.49	1768.64 ± 664.80	3.179	0.001*
Omega-6/omega-3 ratio	14.88 ± 11.29	5.37 ± 1.53	4.713	<0.001*
Cognitive function scores				
Verbal	97.73 ± 17.90	101.75 ± 14.0	0.845	0.402
Quantitative reasoning	109.13 ± 18.35	112.30 ± 9.91	0.788	0.435
Visual-spatial processing	103.27 ± 18.99	114.90 ± 12.08	2.647	0.011*
Working memory	119.73 ± 20.75	139.10 ± 16.30	3.510	0.001*
Total IQ %	109.10 ± 18.27	120.30 ± 11.36	2.671	0.010*
P300 event-related potentials				
P300 latency (ms)				
Fz	318.91 ± 50.31	286.02 ± 43.06	2.395	0.021*
Cz	311.05 ± 41.47	275.77 ± 33.08	4.121	<0.0001*
Pz	321.08 ± 38.56	284.85 ± 55.67	4.802	<0.0001*
P300 amplitudes (mv)				
Fz	9.34 ± 7.24	12.6 ± 5.53	−2.238	0.016*
Cz	7.328 ± 3.412	11.745 ± 3.598	−5.452	<0.0001*
Pz	8.532 ± 4.567	11.623 ± 3.639	−4.675	<0.0001*

* Statistically significant.
IQ, intelligence quotient; SD, standard deviation.

had achieved control of seizures in 23 patients (76.7%), while seizures remained uncontrolled in the rest of the patients despite having received optimal doses of a combination of drugs (confirmed by serum drug levels) for at least 6 months. The control group included 9 boys and 11 girls. The case and control groups were homogeneous in regard to age and sex. We matched the controls for other confounders that could impact IQ, including parental educational attainment, socioeconomic status, nutrition, and level of education of the child (Table 1). All participants in the study had similar diets of ordinary traditional foods.

The comparison of demographic data, omega fatty acid serum levels, cognitive function scores and P300 event-related potentials in children with epilepsy versus healthy controls showed that children with epilepsy had significantly lower levels of omega-3 and higher levels of omega-6 fatty acids, impaired visual-spatial processing and working memory and significant lower IQ values, a significantly longer P300 latency and a lower P300 amplitude compared to their healthy peers (Table 1).

We found that the P300 latency at the frontal cortex and the Stanford-Binet scores were significantly and negatively correlated to omega-3 serum levels and significantly and positively correlated to omega-6 serum levels (Tables 2 and 3).

We found no significant association between the omega-3/omega-6 ratio and patient sex, level of education, socioeconomic status, type of epilepsy, level of seizure control or the antiepileptic treatment used (Table 4).

Discussion

Epilepsy is a chronic disorder with a significant impact on cognitive function[15]; however, the relationship between

Table 2 Correlation between omega-3, omega-6 and omega-6/omega-3 ratio and cognitive function scores in children with epilepsy ($n = 30$).

	Omega-3		Omega-6		Omega-6/omega-3 ratio	
	r	*P*	*r*	*P*	*r*	*P*
Verbal	0.489	0.006*	−0.348	0.060	−0.638	<0.0001*
Quantitative reasoning	0.449	0.013*	−0.301	0.106	−0.593	0.0001*
Visual-spatial processing	0.590	0.001*	−0.179	0.344	−0.602	<0.0001*
Working memory	0.547	0.002*	−0.362	0.049*	−0.662	<0.0001*
Total IQ %	0.668	<0.001*	−0.402	0.028*	−0.807	<0.0001*

* Statistically significant.
IQ, intelligence quotient.

Table 3 Correlation between omega-3, omega-6 and omega-6/omega-3 ratio and P300 parameters in children with epilepsy ($n = 30$).

P300 parameter	Omega-3		Omega-6		Omega-6/omega-3 ratio	
	r	*P*	*r*	*P*	*r*	*P*
Latency						
Fz (m)	−0.426	0.019*	0.113	0.553	0.489	0.006*
Cz (m)	−0.270	0.150	0.238	0.205	0.337	0.068
Pz (m)	−0.283	0.130	0.316	0.089	0.315	0.090
Amplitude						
Fz (μ)	−0.027	0.888	0.198	0.294	0.055	0.773
Cz (μ)	−0.180	0.341	0.260	0.165	0.274	0.142
Pz (μ)	−0.072	0.706	0.131	0.490	0.049	0.798

* Statistically significant.

Table 4 Association between the omega-6/omega-3 ratio and clinical and demographic variables.

	Omega-6/omega-3 ratio	
	Mean ± SD	Independent *t* test/Mann Whitney *U* test
Sex		
Male ($n = 21$)	12.644 ± 7.694	$t = -1.302$
Female ($n = 9$)	20.108 ± 16.434	$P = 0.223$
Education		
Primary education ($n = 12$)	14.392 ± 8.675	$t = -0.207$
Secondary education ($n = 18$)	15.211 ± 12.977	$P = 0.837$
Socioeconomic status		
Middle ($n = 20$)	12.902 ± 7.801	$t = -1.111$
Low ($n = 10$)	18.847 ± 15.999	$P = .290$
Type of epilepsy		
Focal ($n = 13$)	12.577 ± 8.108	$t = -1.206$
Generalized ($n = 17$)	17.901 ± 14.245	$P = 0.243$
Level of seizure control		
Controlled ($n = 23$)	12.092 ± 7.577	$t = -1.843$
Uncontrolled ($n = 7$)	24.055 ± 16.656	$P = 0.109$
Antiepileptic drugs		
Monotherapy ($n = 20$)	18.348 ± 6.759	$t = 0.843$
Polytherapy ($n = 10$)	16.387 ± 7.498	$P = 0.499$

epilepsy and cognitive impairment is complex. In our study, we only included children with idiopathic epilepsy. We excluded children with underlying neurologic, psychological or developmental disorders or receiving chronic medication other than antiepileptic drugs from the study, as we aimed to investigate the effects of epilepsy alone in the absence of confounders that could also cause cognitive impairment in these children.

In our study, epileptic children had significant lower scores for visual-spatial processing, working memory and total IQ compared to healthy children. This was consistent with the study by Dahab et al.,[16] who found statistically significant lower cognitive ability scores in epileptic children compared to children without epilepsy. Sarhan et al.[17] concluded that childhood epilepsy is associated with cognitive deficits and intellectual decline, which are multifactorial comorbidities. Epileptic children exhibited significant delays in cognitive, social, and communication development, had lower IQ scores and were more likely to have attention problems. Barr[18] found that more than half of patients with epilepsy reported subjective disturbances of cognition and memory, while objective neuropsychological tests demonstrated impairment in a comparable proportion.

Our study also demonstrated significant delayed latencies and lower P300 amplitudes in ERPs in children with epilepsy, which reflect an impairment in attention-based auditory cognitive processing. This is consistent with the findings of Casali et al.,[19] who reported prolonged latencies and reduced amplitudes in children with epilepsy. Takhirovna et al.[20] found significant increases in the N200 and P300 latencies and the P300 − N200 interval, which suggests the presence of cognitive disorders in epilepsy.

The P300 component of ERPs can be used during psychometric tests to assess learning and memory recall, particularly in educational institutions to help predict academic performance.[21] The P300 component provides information about the neurophysiological substrate of cognitive processes such as memory, attention, auditory discrimination, sequential information processing and decision making. This waveform does not depend on the physical characteristics of the sensory input, but instead is influenced by the cognitive task that is being performed.[22] The P300 wave latency is directly correlated to information processing speed. On the other hand, the P300 amplitude indicates the extent of the resources allocated to perform a specific neurocognitive process, as it reflects the number of fibres activated in the task. A decreased P300 amplitude or an increased P300 latency are indicative of deficits in cognitive processing of sensory information.[12]

Cognitive impairment in children with epilepsy may result from epileptogenesis itself or be a side effect of antiepileptic medication.[23] In our study, we matched controls to cases for confounders that could have an impact on cognition, including parental educational attainment, socioeconomic status, nutrition, and the level of education of the child.

Evidence from previous animal[24] and human studies[25] suggests that omega-3 fatty acid deficiency could be a mechanism of cognitive impairment. Animal studies have shown that omega-3 fatty acids may play a role in cognitive development and their deficiency impairs the ability to respond to environmental stimuli, with omega-3-deficient rats performing poorly in learning and memory tasks in various tests.[26] This is supported by evidence from human studies that found improvements in cognitive function with omega-3 supplementation.[27] Adequate intake of polyunsaturated fatty acids has been associated with subsequent improvements in various areas, including problem-solving skills and functional activity in cortical attention networks in school children.[28] Another study in children aged 7–9 years that received an omega-3-enriched diet for six months found significant improvements in verbal learning, spelling and reading scores.[29]

However, changes in the omega-3 to omega-6 ratio might have a greater influence on the nervous system than the levels of either fatty acid in isolation.[7] Our study found significantly altered omega-3 to omega-6 fatty acid ratios in children with epilepsy that were not related to the clinical manifestations of epilepsy. Furthermore, all the children in the study had similar diets. The abnormal omega-6 to omega-3 ratio in children with epilepsy may be due to inadequate supplementation or to increased use of omega-3 fatty acids to overcome oxidative stress and reduce neuronal cell inflammation. The modern diet is very unbalanced, with an estimated average omega-6/omega-3 ratio of 20:1. The current evidence suggests that there is an association between imbalances in the omega-6/omega-3 ratio in brain tissue and several neuropsychiatric disorders.[30] There is no evidence suggesting that antiepileptic drugs affect the metabolism or utilization of either omega-3 or omega-6 fatty acids. Instead, several studies have highlighted the beneficial effect of omega-3 and omega-6 supplementation at appropriate doses to improve seizure control in drug-resistant epilepsy.[31]

Our study revealed a significant positive correlation between omega-3 levels and cognitive function scores, while we found a negative correlation between cognitive function scores and omega-6 levels and the omega 6/omega 3 ratio. Jumpsen et al.[32] found that during neuronal and glial cell development, even small changes in the ratio of omega-6 to omega-3 in the diet have significant effects on development. Their study showed that a ratio of 4:1 was optimal for the development of the frontal cortex, hippocampus, cerebellum and glial cell number. Yehuda[33] also found that a mixture of linoleic (omega-6) and alpha-linolenic acids (omega-3) at a 4:1 ratio was most effective in improving learning performance.

We found a significant negative correlation between omega-3 levels and the P300 latency and a significant positive correlation between the omega-6/omega-3 ratio and the P300 latency. However, this correlation was only significant at the frontal cortex. The frontal lobe is responsible for executive and higher-order cognitive functions, including sustained attention, planning and problem solving. Thus, maintaining optimum lipid levels and ratios in this region of the brain is critical.[34]

Konagai et al.[35] compared event-related potential measurements in subjects before and after supplementation with fish oil for 35 days, and reported improvement in attention functions, particularly those involving complex cortical processing, after ingestion of omega-3 fatty acids. These results reflected the impact of omega-3 fatty acids on the activity of the central nervous system through the improvements in reaction time, attention and cognitive performance

as well as improvements in mood and changes in certain neuroelectrical parameters.[36]

There are several limitations to consider in interpreting the findings of our study, such as the small sample size, which limits internal validity of our findings. Also, we were unable to compare cognitive function in individuals with an optimal omega-6/omega-3 ratio compared to individuals with an imbalanced ratio, as all children with epilepsy in our sample had ratios that exceeded 4:1. Therefore, further longitudinal studies are required to evaluate the impact of nutritional intervention to maintain a balanced omega-6/omega-3 ratio on cognitive function in children with epilepsy. The strengths of our study include the assessment of cognitive function through 2 different psychological tests to prevent interrater biases.

Conclusion

Based on our findings, we conclude that children with epilepsy have abnormal omega-3 to omega-6 serum level ratios, which is associated with cognitive impairment. Early detection of cognitive impairment and proper intervention are necessary to improve quality of life and prevent learning disabilities and social problems in these children. Further studies are required to assess the effect of omega-3 supplementation on cognitive function in children with epilepsy.

Conflicts of interest

The authors declare no conflicts of interest.

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