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Evaluation of the effect of anti-epileptic drugs on serum immunoglobulin levels in children with epilepsy

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Abstract

Introduction: Most antiepileptic drugs may have side effects such as behavioral disorders and immunological changes, which can affect serum levels of immunoglobulins.
Objective: To study the effect of anticonvulsant drugs on serum levels immunoglobulins in children referred to the Taleghani educational center of Gorgan during 2015-2016.
Patients and Methods: All pediatric patients with the first seizure experience diagnosed with diagnostic procedures such as history, physical examination and electroencephalography were diagnosed and treated with phenobarbital or levetiracetam were included. At first and at the end of the study, 5 cc blood samples were taken for measuring serum IgA, IgM, IgG and IgE levels. The time between two blood sampling was six months. Data were analyzed using SPSS version 18 software.
Results: A total of 179 children were enrolled in the study, of which 104 (58.1%) were male and 75 (41.9%) were female. Around 78 (43.6%) were treated with levetiracetam and 101 (56.4%) were treated phenobarbital. The mean age of the patients was 3.33 ± 1.21 years. Based on statistical tests, the significant effect of both drugs on all indices was significant, which in all cases reduced the level of immunoglobulins. Additionally, the effect of drugs or, in other words, the amount of changes caused by them on different indices in terms of drug used was also investigated, which results showed no significant difference between the effect of the two drugs.
Conclusion: From the results of this study, it can be concluded that both levetiracetam and phenobarbital have potentially influenced the immunoglobulins with the same effect. The results of this study may indicate the need to pay attention to the vulnerability of these children to various types of infections.

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Introduction

Epilepsy and seizure syndromes are common diseases, which their prevalence has increased over the past few years and have become a worrisome factor in health management assemblies (1). Epilepsy is one of the most common neurological disorders among children under the age of sixteen (2,3), which is one of the most important factors in children's growth and developmental abilities and is one of the most important causes of intellectual disability in children (4,5). Additionally, patients with epilepsy have a high risk of sudden death and are associated with overall high risk of death (6-9).

In recent years, we have faced a growing trend in the diagnosis and treatment of this disorder. Most of the anticonvulsants currently that are used include carbamazepine, phenobarbital, sodium valproate, phenytoin and recently levetiracetam. Although these anticonvulsants are good drugs to control the disease in a satisfactory way, these drugs may also have side effects that include behavioral disorders and immunological changes affecting serum levels of immunoglobulins (9, 10). Studies have shown that these drugs affect both humoral and cellular immune systems (2).

Key point

Anticonvulsant drugs may decrease serum immunoglobulin levels and result in secondary immunodeficiency. Physicians should check serum immunoglobulin serially in the patients who are taking these medicines.

The role of the mechanism of inflammation and inflammatory processes has been demonstrated in the development, evolution and sustainability of epilepsy. Some antiepileptic drugs can directly affect both cellular and humoral immune systems, improve or modify the expression of some of the immune molecules, or directly affect the production or reduction of some cytokines production. This effect on

regulatory mechanisms may be due to the direct effect of anticonvulsant drugs on the status of the activity of the transcriptional system, in particular the nuclear factor-kappa B factor. However, the current information available for proper judgment is not enough (10-13).

Numerous studies have been conducted on the effects of anticonvulsant drugs on the human immune system. The results of these studies are in some cases interspersed with each other and contradict in many cases. Most of these studies have been performed on first-generation drugs for seizure therapy (1,2,5,14-16).

There are several issues in this regard. First, the effect of drugs on the immune system cannot be well- differentiated from the effect of seizure on the immune system. Secondly, first-generation drugs are much more used than new-generation drugs for treatment and maybe the effects of a new generation of drugs have not been well-considered. Third, some of these changes in the immune system may not have been due to drug use and are due to side effects or possible responses of the body to the drug, like antiepileptic hypersensitivity syndrome (2).

Have shown that anticonvulsants can reduce the level of immunoglobulins in children treated with these drugs. Among anticonvulsants, phenytoin has a known effect on serum immunoglobulin levels (15-12, 19, and 18). The most commonly known immunoglobulin in this field is IgA, which is particularly reduced in the treatment with phenytoin (16,23-20). Carbamazepine and sodium valproate also have a decreasing effect on the serum immunoglobulin levels (17,20-24).

Phenobarbital is one of the most commonly used drugs in the treatment of pediatric seizures, and a high percentage of patients with seizure used a course of phenobarbital treatment during their treatment and was selected as a relatively safe drug in this study. Levetiracetam is also a new anti-seizure medication that had significant positive therapeutic effects in several studies. On the other hand, the incidence of its complications has been less than other anti-seizure medications such as phenytoin and diazepam (3).

Given that the childhood immune system has not yet reached its full maturity and ultimate strength, it is vulnerable to long-term and malignant effects of their immune system will cause irreparable complications in the future. The presence and production of immunoglobulins in the pediatric body is a factor in consolidating and strengthening the immune system's activity in the short and long term. Naturally, any changes in the regulation of this system, such as decreasing, increasing or damaging and changing in the structure of immunoglobulins, can have adverse effects on it.

Among these secondary complications, the immune system can be weakened by the presence of infectious diseases, the development of pro-malignant and malignant diseases. Therefore, in diseases like epilepsy, which the child should take medically at an early age, it is possible to have serious adverse effects in adolescence.

Objectives

Considering the contradictory results of various studies on the effect of anticonvulsants on the human immune system, and given the high consumption of these drugs in the pediatric population, we aimed to study the effect of the anti-seizure drugs, levetiracetam and phenobarbital on the serum levels of immunoglobulins in children referred to the Taleghani educational center in Gorgan in 1395.

Patients and Methods

Study design

This cross-sectional descriptive-analytic study was carried out on patients aged 12-2 years old referred to the Pediatric neurology clinic of Taleghani hospital in Gorgan during 2015-2016. All pediatric patients with the first seizure experience followed by diagnostic procedures such as taking history, physical examination, and electroencephalography and treated with phenobarbital or, levetiracetam were entered the study.

Exclusion criteria include patients receiving immunosuppressive drugs, taking any medication other than the drugs mentioned in the study, having any infection during the study period, children under 2 years old, as the deficiency of IgA, IgM, IgG and IgE less than normal range for age at the beginning of the study.

In this study, 2 blood samples were taken from patients. One time at the beginning of the study and one time at the end of the study. Around 5cc blood samples were taken for extraction of plasma and measurement of serum IgA, IgM, IgG and IgE levels and were kept in freezing at -80°C in the laboratory of Taleghani hospital.

The interval between blood sampling was six months. Then the patients were treated with one or more anticonvulsants based on the diagnosis and opinion of their physician. A significant decrease in serum levels of immunoglobulins was considered as lower than the fifth percentile for the age during the study (18).

This study did not have any physical, psychological or financial harm to the subjects, and is in accordance with the ethics committee's of Golestan university of medical sciences. By explaining the goals and benefits of the study, the participation rate of children and their parents was increased.

Data analysis

The data were analyzed by SPSS-18 software and statistical results were analyzed using descriptive indexes including mean, standard deviation, frequency and percentage. Student *t* test, one-way ANOVA and chi-square test were used to analyze the data. *P* values less than 0.05 were considered significant.

Results

In this study, a total of 179 children were enrolled in the study, of which 104 (58.1%) were male and 75 (41.9%) were female.

The mean age of the patients was 3.33±1.21 years. The mean age of patients treated with levetiracetam was 3.00 ± 0.88 years and the mean age of patients treated with phenobarbital was 3.58 ± 1.36 years old. Of patients, 78 (43.6%) were treated with levetiracetam and 101 (56.4%) were treated with phenobarbital. The frequency of drugs used by patients was analyzed by gender and according to the chi-square test; there were no differences between the two groups ($P=0.479$).

The descriptive statistics including mean, median, standard deviation, the lowest and highest laboratory marker values for immunoglobulins in the levetiracetam group were investigated, the results were shown in Table 1, since these values were evaluated for the phenobarbital group which is shown in Table 2. When the distribution of data is normal, independent *t* test is used for comparison; otherwise the Mann-Whitney U and Wilcoxon are used.

According to the Shapiro-Wilk test, only the IgM variable in the levetiracetam drug has a normal distribution before and after the intervention, which is used to compare the paired *t* test, and in the rest of all the variables there was no normality in distribution (*P* value is less than 0.05 and the assumption of normalization is rejected), then Wilcoxon test is used for comparison.

Additionally, the effect level (the difference in the amount of pre-treatment and after treatment in each index) was reported by type of drug (Tables 3 and Table 4). Then, to compare these indices before and after the intervention by drug distinction, first the normality of distribution of data was evaluated by using Shapiro-Wilk test and if any index was normal before and after treatment, then paired *t* test was used and otherwise Wilcoxon test was used.

The mean and standard deviation of the studied indices in patients are presented in terms of the drugs (Table 5 and Table 6). Based on the statistical tests, the effect of both drugs on all indices significantly reduced the level of immunoglobulins in all cases.

The effect of drugs, or, in other words, the amount of changes made to the various indexes in terms of the drug used is shown in Table 7. In the previous analysis, it was shown that both drugs are effective and are now compared to show which drugs are most effective.

The result of Mann-Whitney U test shows no significant difference between the effect of the two drugs. Hence, in general, one can conclude that both drugs are effective in all variables but have the same effect and there is no difference between the two drugs.

Discussion

This cross-sectional descriptive-analytic study was carried out on patients aged 2-12 years old. All pediatric patients with the first seizure experience followed by diagnostic procedures such as taking history, physical examination, and electroencephalography and treated with phenobarbital or, levetiracetam were entered the study.

In this study, a total of 179 children were enrolled in the study, of which 104 (58.1%) were male and 75 (41.9%) were female. Of the patients, 78 (43.6%) were treated with levetiracetam and 101 (56.4%) were treated with phenobarbital. The mean age of the patients was 3.33 ± 1.21 years. The mean age of patients treated with levetiracetam was 3.00 ± 0.88 years and the mean age of patients treated with phenobarbital was 3.58 ± 1.36 years old. The mean and standard deviation of the studied indices (immunoglobulins) were evaluated among the patients in terms of the drug used. Based on statistical tests, the significant effect of both drugs on all indices was clearly significant, which in all cases reduced the level of immunoglobulins.

Additionally, the effect of drugs or, in other words, the amount of changes caused by them in different indices was also examined, which results showed no significant difference between the effects of the two drugs. In a systematic review study by Beghi et al (3), sodium valproate did not significantly affect the level of serum immunoglobulins. The use of carbamazepine in some studies has been associated with an increase in serum immunoglobulins such as IgA, IgM and IgG, and in some studies, it has no effect on the serum levels of these three immunoglobulins. Phenytoin also causes IgA reversible deficiency. In this study, it has been reported that it has anti-inflammatory effects, however there is no evidence of a reduction in serum immunoglobulins. The results of these studies are not consistent with our study on levetiracetam, because in our study, this drug has a

Table 1. Descriptive statistics of measured parameters before and after treatment in the levetiracetam group

	IgA	IgM	IgG	IgE	IgA	IgM	IgG	IgE
	Before	Before	Before	Before	After	After	After	After
Mean	0.60	0.92	8.72	31.00	0.52	0.86	8.46	26.61
Median	0.56	0.91	8.90	28.00	0.48	0.87	8.70	24.00
Standard deviation	0.22	0.21	1.34	13.36	0.17	0.20	1.15	11.22
Minimum	0.33	0.38	5.30	11.50	0.32	0.34	5.80	10.50
Maximum	1.20	1.60	11.00	68.00	0.97	1.40	11.00	64.00

Table 2. Descriptive statistics of measured parameters before and after treatment in the phenobarbital group

	IgA	IgM	IgG	IgE	IgA	IgM	IgG	IgE
	Before	Before	Before	Before	After	After	After	After
Mean	0.63	0.91	8.19	32.01	0.55	0.86	8.08	26.78
Median	0.52	0.91	8.50	25.00	0.48	0.87	8.20	22.00
Standard deviation	0.33	0.29	1.54	19.12	0.28	0.20	1.30	14.28
Minimum	0.31	0.22	2.30	11.90	0.30	0.34	5.10	10.00
Maximum	2.10	1.98	10.80	100.00	2.35	1.40	12.00	78.00

Table 3. Descriptive statistics of change in the indexes in the levetiracetam-treated group

	IgA	IgM	IgG	IgE
Mean	0.082	0.061	0.26	4.39
Median	0.070	0.070	0.10	3.00
Standard deviation	0.086	0.110	0.840	4.95
Minimum	-0.06	-0.51	-1.70	-3.00
Maximum	0.36	0.35	3.30	22.50

Table 4. Descriptive statistics of change in the indexes in the phenobarbital -treated group

	IgA	IgM	IgG	IgE
Mean	0.085	0.053	0.10	5.23
Median	0.050	0.040	0.10	3.20
Standard deviation	0.152	0.175	0.97	9.91
Minimum	-0.56	-0.92	-6.30	-6.00
Maximum	0.91	0.70	3.00	48.00

Table 5. Results of the mean and standard deviation of the indices studied among patients treated with levetiracetam

		Mean	Standard deviation	*P* value
Pair 1	IgA before	0.60	0.22	0.0001[a]
	IgA after	0.52	0.17	
Pair 2	IgM before	0.92	0.21	0.0001[b]
	IgM after	0.86	0.20	
Pair 3	IgG before	8.72	1.34	0.011 [a]
	IgG after	8.46	1.15	
Pair 4	IgE before	31.00	13.36	0.0001 [a]
	IgE after	26.61	11.22	

[a] Wilcoxon test; [b] Paired samples *t* test.

Table 6. Results of the mean and standard deviation of the indices studied among patients treated with phenobarbital

		Mean	Standard deviation	*P* value
Pair 1	IgA before	0.63	0.33	0.000[a]
	IgA after	0.55	0.28	
Pair 2	IgM before	0.91	0.29	0.000[a]
	IgM after	0.86	0.22	
Pair 3	IgG before	8.19	1.54	0.046[a]
	IgG after	8.08	1.30	
Pair 4	IgE before	32.01	19.12	0.000[a]
	IgE after	26.78	14.28	

[a] Wilcoxon test.

reduction effect on serum immunoglobulins level.

Another difference with our study was about the type of anticonvulsant drug that administered and has not been matched by our study, while the differences can be attributed to this fact and the differences in the design of other studies with our study. In addition, some studies have found that the reduction in serum immunoglobulins is a cause for susceptibility to infections when taking anticonvulsants (15).

Svalheim et al (21) showed low levels of immunoglobulins in epileptic patients treated with lamotrigine or carbamazepine. These two drugs decrease total levels IgG and IgG1 in both genders. Levetiracetam did not change the levels of immunoglobulin in treated patients versus control group. The results of this study are not consistent with our study. In another study by Callenbach et al (25), the status of immunoglobulins in children with epilepsy was studied. This study showed that when taking anticonvulsant, IgA, IgG1, IgG2 and IgG4 concentrations in comparison with healthy subjects were significantly higher than reported values for healthy subjects. In a group of 127 children, the Ig level at the time of starting the drug was compared with those who used anticonvulsant drugs for 9-18 months. Results showed that IgA and IgG4 levels decreased significantly compared to normal concentrations, however the IgG1 and IgG3 levels increased significantly. To determine the effect of anti-epileptic drugs, Ig levels in children undergoing single-drug treatment with carbamazepine or valproic acid were separately analyzed. The use of carbamazepine was associated with a significant decrease in IgA and IgG4 levels and the use of valproic acid was associated with a significant decrease in IgA and elevated IgG1 levels. The difference between this study and our study was in the type of drugs that were used and was not similar to our study, however Indicating a decrease in immunoglobulins, and another difference in our study with our study was that in our study, subtypes of each immunoglobulin have not been studied and it is suggested to be investigated in future studies. The existing differences and contradictions between our study and other studies can be due to differences in the type of study design and the type of drug used by patients, and given the inconsistency and uncertainty about the results, further study is necessary.

Table 7. The effect of drugs or, in other words, the rate of change in the various indexes in terms of the drug used

		Mean	Standard deviation	*P* value[a]
IgA	Levetiracetam	0.082	0.085	0.777
	Phenobarbital	0.085	0.15	
IgM	Levetiracetam	0.061	0.11	0.444
	Phenobarbital	0.053	0.17	
IgG	Levetiracetam	0.26	0.8	0.576
	Phenobarbital	0.10	0.97	
IgE	Levetiracetam	4.39	4.95	0.951
	Phenobarbital	5.23	7.91	

[a] Mann-Whitney test.

Conclusion

From the results of this study, it can be concluded that both levetiracetam and phenobarbital have potentially influenced immunoglobulins and the immune system in general, but have equal effect without significant difference. The results of our study may indicate the need to pay attention to the vulnerability of these children to various types of infections, and in order to prevent this, the physician should consider the necessary treatment plans. Finally, it is suggested that studies with a larger sample size, longer duration, and more investigations with more antiepileptic drugs should be performed to obtain more accurate and more general results.

Limitation of study

There are two major limitations in this study that could be addressed in future research. First; low sample size in our study, and we think and advise other researchers need to base the same study on a larger sample size to end up with more accurate results. The second problem is time limitation, this study is based on a thesis for residency degree.

Authors, Contribution

Conceptualization: Arash Kalantari, Zeynab Bagheri.
Data curation: Arash Kalantari, Zeynab Bagheri.
Formal analysis: Arash Kalantari, Zeynab Bagheri.
Investigation: Zeynab Bagheri.
Methodology: Arash Kalantari, Seyed Ahmad Hosseini.
Project administration: Zeynab Bagheri.
Resources: Arash Kalantari, Seyed Ahmad Hosseini.
Software: Arash Kalantari, Seyed Ahmad Hosseini.
Supervision: Zeynab Bagheri.
Validation: Arash Kalantari, Seyed Ahmad Hosseini.
Visualization: Zeynab Bagheri.
Writing–original draft: Arash Kalantari, Zeynab Bagheri, Seyed Ahmad Hosseini.
Writing–review & editing: Arash Kalantari, Zeynab Bagheri, Seyed Ahmad Hosseini.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Golestsn University of Medical Sciences approved this study. The institutional ethical committee at Golestan University of Medical Sciences approved all study protocols (IR.GOUMS.REC.1395.191). Accordingly, written informed consent was taken from all participants or their parents before any intervention. This study was extracted from M.D thesis of Zeynab Bagheri for degree of residency at this university (Thesis #215). Additionally, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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