Correlation between serum level of Immunoglobulin and antiepileptic drugs in sample of Egyptian Epileptic Patients.

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Abstract: Background: Data on the effects of antiepileptic drugs on immune system are frequently inconsistent and some time conflicting because the affects of drugs cannot be separated from those of seizures, first-generation drugs have been most intensively investigated, the genetic background of the patients, the mechanism of action and pharmacokinetics profile of the AEDs may act as confounders. Valproate, carbamazepine, phenytoin, vigabtrin, levetiracetam and diazepam have been found to modulate the immune system activities by affecting hurmoral and cellular immunity. AEDs are associated with pharmacokinetics interactions (most frequently occurring with carbamazepine, phenytoin, Phenobarbital and valproate). Hepatic metabolism is the primary side of interaction for AEDs. An important adverse effect of the action of AEDs on the immune system is antiepileptic hypersensitivity syndrome (AHS). The pathological mechanism of the effects of AEDs on immune system are incompletely understood. **Aim of work:** To investigate serum immunoglobulin IgG, IgA and IgG concentrations in patients with focal epilepsy, shortly after first presentation of one or more unprovoked epileptic seizures before the start the treatment with AEDs, and compared them with patients treated with three different antiepileptic drugs carbamazepine (CBZ), Sodium valproate (VPA) and Levetiracetam (LEV) in monotherapy and in polytherapy, for at least three months of drug intake duration. **Patient and Methods:** This cross sectional descriptive study conducted in the epilepsy clinic, department of Neurology, Ain Shams University. This present study aimed at describing data of 82 patients with focal epilepsy based on clinical course, EEG report and MRI brain images who attended the epilepsy clinic over a year period from, February 2018 to February 2019. Plasme Immunoglobulin levels were measured with guantitative methods using a Biosystems kits and is presented as mg/dL. **Results:** A total 82 subjects in the age range of 13-53 years old met the inclusion and exclusion criteria of this study. Serum level of IgG, IgA and IgM is not altered in patients shortly after the first presentation with epileptic seizures and before start treatment with antiepileptic drugs. Significant reduction in serum level of IgG and IgA was detected after treatment with Carbamazepine in monotherapy and in combination with sodium valproate and levetiracetam. Low serum level of IgM was found after treatment with carbamazepine in monotherapy and in combination with valproate only. Normal serum level of IgG, IgA and IgM was detected after treatment with valproate. **Conclusion:** This study indicated that carbamazapine in monotherapy and in combination with valproate and levetiracetam decrease serum levels of Immunoglobulin in patients with focal epilepsy. However, humoral immunity was not altered in patients shortly after the first presentation with epileptic seizures and before the start the treatment with AEDs. Professionals who frequently prescribe these drugs should be alert to this alteration. Although in our study, patients with immunoglobulin deficiency were asymptomatic, assessment of serum immunoglobulin levels should be done at starting the administration of AEDs and in serial intervals afterward in epileptic patients. Recurrent seizures are a significant cause of morbidity, we conclude that intravenous immunoglobulin (IVIG) is a safe therapy and may have beneficial effects in intractable epilepsies. More studies should be carried out to support the efficacy of IVIG in the treatment of intractable epilepsy and to elucidate the pathogenesis and the effects of this therapy, ideal dosage and treatment schedules should be define.

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1. Introduction:

Epilepsy is not a specific disease or even a single syndrome, but rather a broad category of symptom complexes arising from any number of disordered brain functions that themselves may be secondary to a variety of pathologic processes. Hughlings Jackson was the first to define epileptic seizure; the clinical manifestations are sudden and transient and can include a wide variety of motor, psychic and sensory phenomena, with or without alteration in

consciousness or awareness ***(Shorvon, 2000).*** Antiepileptic drugs (AEDs) are the cornerstone in epilepsy treatment. When medication for epilepsy is introduced, it may have to be continued for many years, sometimes throughout life. Antiepileptic drugs are in a very common use not only for epilepsy, but also in psychiatry as mood stabilizers, for the treatment of neuropathic pain, and for migraine prophylaxis. The side effects of these drugs are very important; some adverse effects develop insidiously over time and are often not noticed during the initial phase. Nevertheless, such side effects can have hazardous consequences for health and quality of life over time. Increasing of evidence indicated that beside the central nervous system, antiepileptic drugs may also affect the immune system. Experimental data showed that classical and newer antiepileptic drugs affect peripheral immunological parameters ***(Patsalos & Bourgeois, 2010)***.

Immunologic Effects of Antiepileptic Drugs:

AEDs can directly affect both humoral and cellular immunity, modifying the expression and the synthesis of some molecules, mainly cytokines. The mechanisms of the effects are often not understood. It is often difficult to discriminate between the effects of AEDs and those of seizures or other, potentially confounding factors (e.g., undercurrent illness). Some data suggest that AEDs can modulate the immune system activity, and may, therefore, either increase or reduce the epileptic threshold.

Valproate: No consistent data are available about valproate effects on the immune system. Some revealed that the production of cytokines [e.g., tumor necrosis factor (TNF) and interleukin (IL)-6] by monocytes and glia was decreased; this effect is probably due to an inhibitory action of valproate on NF-kB translocation to the nucleus. Conducted research on 10 healthy volunteers who were treated with valproate, and on the seventh day of therapy, all of them had significantly higher serum levels of IL-6. It was reported in a case series of pediatric patients an increase in serum levels of IL-1a, IL-1b, and IL-6, whereas IL-2 production was unchanged ***(Verrotti et al., 2010).***

Carbamazepine: A Study showed an increase in IL-1a, IL-1b, IL-2, and IL-6 serum levels in pediatric patients after 1 year of AED therapy. Comparing cytokine levels before and after carbamazepine. More equivocal are the results concerning carbamazepine and immunoglobulin (Ig) serum level modification, as both increased and decreased IgA, IgM, and IgG levels are reported. 39 adult patients treated with carbamazepine for 2 years, comparing them with a control group of 40 healthy nonsmokers: The serum levels of IgA, IgG, and IgM in control subjects did not differ significantly from those obtained from carbamazepine-treated patients; there was, in addition, a significant increase in cytotoxic activity of NK cells in the carbamazepine group as compared with controls. Isolated cases with drug induced immunoglobulin deficiency are recorded ***(Verrotti et al., 2010).***

Phenytoin: This drug can provoke a decrease of suppressor T cells and a reversible IgA deficiency in patients with epilepsy. The gingival overgrowth is probably due to the increased production of both IL-6 and IL-8, combined with elevations of basic fibroblast growth factor as observed in vitro using human gingival fibroblasts; this increase contributes to an enhanced recruitment and activation of inflammatory cells and thereby provides the background for the establishment of an interaction between cytokines and periodontal connective tissue cells ***(Sume et al., 2010).***

Vigabatrin: There are some data demonstrating that vigabatrin can interfere with the cellular immune response. 29 pediatric patients were studied after 1 and 3 months of treatment with vigabatrin, found that the percentage and absolute number of T and B lymphocytes, T-helper–inducer lymphocytes, and T-rosetting lymphocytes were not significantly different in controls and in children with epilepsy before and after treatment; that the percentage and absolute number of T cytotoxic-suppressor lymphocytes and NK cells were significantly increased after l and 3 months of treatment with vigabatrin; and that the serum levels of IgA, IgG, and IgM did not differ significantly from those of the control group ***(Friedman & Dingledine, 2011).***

Levetiracetam: Data on the effect of levetiracetam on the immune system are sparse. Recently, the effects of levetiracetam on IL-1b system in the hippocampus and pyriform cortex of chronic epileptic rats was studied, found that levetiracetam reduced reactive gliosis and expression levels of IL-1bsystem in the hippocampus and the pyriform cortex. These findings suggest that levetiracetam may have, at least in part, anti-inflammatory effects, particularly against IL-1b system in neuroglia within epileptic brain ***(Friedman & Dingledine, 2011).***

Diazepam: It was reported that diazepam inhibits human T-cell function through peripheral benzodiazepine receptors, decreasing interferon (IFN)-c production. It is apparent that IFN-c possesses antiviral and immunomodulatory activities. IFN-c knockout mice showed deficiencies in natural resistance to bacterial, parasitic, and viral infections. In addition to recurrent infection, infants with deficient production of IFN-c exhibited decreased neutrophil mobility and NK cell activity ***(Wei et al., 2010).***

Lamotrigine: There are also reports suggesting that lamotrigine (LTG) may induce

panhypogammaglobulinemia, with low IgA, IgG, and IgM serum level, where the diagnosis of common variable immunodeficiency (CVID) has been proposed. Several cases of panhypogammaglobulinemia, with a phenotype similar to CVID in lamotrigine-treated patients have been noted **(Patsalos, Bourgeois, 2010).**

Aim of work:

To investigate serum immunoglobulin IgG, IgA and IgG concentrations in patients with focal epilepsy, shortly after first presentation of one or more unprovoked epileptic seizures before the start the treatment with AEDs, and compared them with patients treated with three different antiepileptic drugs carbamazepine (CBZ), Sodium valproate (VPA) and Levetiracetam (LEV) in monotherapy and in polytherapy, for at least three months of drug intake duration.

2. Subjects and Methods

Study design:

Descriptive cross sectional study.

Study settings:

Epilepsy neurology clinic of the Neurology department in Ain Shams University hospitals, Cairo, Egypt.

Study Population:

Inclusion Criteria:

Patients were considered for inclusion if they met all of the following criteria:

- Age above 10 years old.
- Had been diagnosed with focal epilepsy, based on clinical course, EEG report and MRI brain image.
- The epilepsy types, EEG finding and MRI brain finding were classified according to the recommendations of the ILAE (Commission on Classification and Terminology of the International League Against Epilepsy 1989).
- They were divided into two groups, first group; 12 patients after first presentation of one or more unprovoked epileptic seizures and before the start of treatment with any AEDs, second group; 70 patients, 20 were on Sodium valproate, 20 were on carbamazepine, 15 were on carbamazepine in combination with valproate, 15 were on carbamazepine in combination with levetiracetam, for at least three months of drug intake duration (all selected patients were free of fits for at least six months).

Exclusion Criteria:

The following exclusion criteria were considered, because of potential effect on plasma immunoglobins level:

- Acute or chronic infections.
- Autoimmune Disorder (Rheumatoid Arthritis, SLE, Scleroderma).
- Cirrhosis.
- Multiple Myeloma.
- Lymphoma or Chronic Lymphocytic Leukemia.
- Smoking.

Sampling Method*:* convenient sampling.

- **Sample Size:** A sample size of 100 cases were participated in this study.

Ethical Considerations:

A written informed consent was obtained from study participants after explanation of the purpose of the study. Anonymity of the subjects was ensured and the results was stored in a secure place with access only to the principal investigator of the study The study was conformed to the standards of the Ethical Review Committee, Ain Shams University.

Study Procedures:

All patients participating in the study were submitted for full general and neurological history and examinations. Every patient had MRI brain image and EEG study. Plasme Immunoglobulins level were measured with Guantitative methods using a Biosystems kits and is presented as mg/dL.

Statistical methods

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013.

Descriptive statistics were done for quantitative data as minimum & maximum of the range as well as mean ± SD (standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage

Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with normally distributed data. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions. While correlations were done using Pearson correlation for numerical parametric data. The level of significance was taken at P value < 0.050 is significant, otherwise is non-significant.

3. Results:

Eighty two patients and twenty control subjects were enrolled in this study and were divided into 6 groups:

- Group (1): Twenty patients on treatment with sodium valproate.
- Group (2): Twenty patients on treatment with carbamazepine.
- Group (3): Fifteen patients on treatment with carbamazepine in combination with valproate.

- Group (4): Fifteen patients on treatment with carbamazepine in combination with levetiracetam.
- Group (5): twelve patients shortly after first presentation of epileptic seizure and before the start of treatment with antiepileptic drugs (AEDs).

Group (6): Eighteen control subjects

Serum Immunoglobulin concentrations among the groups:

The prevalence of low and normal and serum Immunoglobulin (Ig) concentrations in patients with focal epilepsy and control subjects are presented below.

Tables (1): Relation between serum IgG concentration, antiepileptic drugs and control subjects.

Groups	IgG						Chi-Square	
	Normal		Low		Total			
	N	%	N	%	N	%	X^2	*P*-value
Sodium Valproate	20	40.00	0	0.00	20	20.00	100.000	<0.001*
CBZ	0	0.00	20	40.00	20	20.00		
CBZ+Valproate	0	0.00	15	30.00	15	15.00		
CBZ+ LEV	0	0.00	15	30.00	15	15.00		
Before start treatment with AEDs	12	24.00	0	0.00	12	12.00		
Control Subjects	18	36.00	0	0.00	18	18.00		
Total	50	100.00	50	100.00	100	100.00		

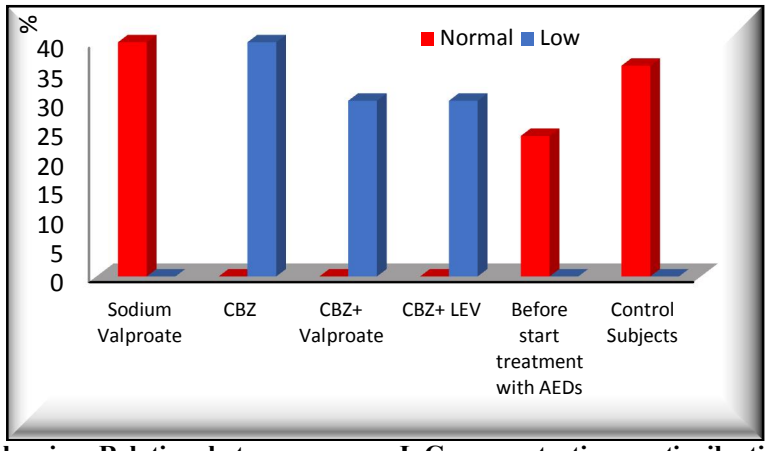

Figure (1): Figure showing Relation between serum IgG concentration, antiepileptic drugs and control subjects.

Patients currently on carbamazepine, combination of carbamazepine with sodium valproate and combination of carbamazepine with levetiracetam, had shown; low level of serum IgG concentration [CBZ=20 (40%), CBZ+Valproate =15 (30%), CBZ+LEV=15 (30%)].

Normal serum level of IgG was found in patients currently on sodium valproate in monotherapy.

Normal serum level of IgG was found in patients shortly after first-presentation of one or more unprovoked epileptic seizure and before the start of treatment with any antiepileptic drugs.

Tables (2): Relation between serum IgA concentration, antiepileptic drugs and control subjects.

Groups	IgA						Chi-Square	
	Normal		Low		Total			
	N	%	N	%	N	%	X^2	P-value
Sodium Valproate	20	38.30	0	0.00	20	20.00	89.094	<0.001*
CBZ	0	0.00	20	39.62	20	20.00		
CBZ+Valproate	0	0.00	15	30.18	15	15.00		
CBZ+ LEV	0	0.00	15	30.18	15	15.00		
Before start treatment with AEDs	12	23.40	0	0.00	12	12.00		
Control Subjects	18	38.30	0	0.00	18	18.00		
Total	47	100.00	53	100.00	100	100.00		

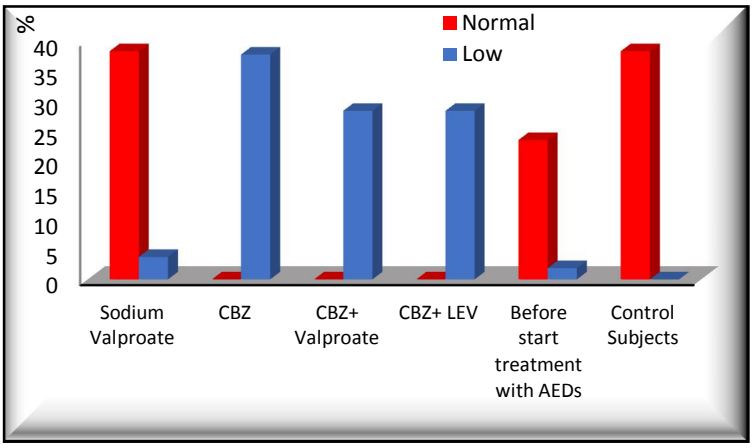

Figure (2): Figure showing Relation between serum IgA concentration, antiepileptic drugs and control subjects.

Patients currently on carbamazepine, combination of carbamazepine with sodium valproate and combination of carbamazepine with levetiracetam, had shown; low level of serum IgA concentration [CBZ=20 (39.62%), CBZ+Valproate =15 (30.18%), CBZ+LEV=15 (30.18%)].

Normal serum level of IgA was found in patients currently on sodium valproate in monotherapy.

Normal serum level of IgA was found in patients shortly after first-presentation of one or more unprovoked epileptic seizure and before the start of treatment with any antiepileptic drugs.

Tables (3): Relation between serum IgM concentration, antiepileptic drugs and control subjects.

Groups	IgM						Chi-Square	
	Normal		Low		Total			
	N	%	N	%	N	%	X^2	P-value
Sodium Valproate	20	31.25	0	0.00	20	20.00	95.949	<0.001*
CBZ	0	0.00	20	55.56	20	20.00		
CBZ+Valproate	0	0.00	15	41.67	15	15.00		
CBZ+ LEV	14	21.88	1	2.78	15	15.00		
Before start treatment with AEDs	12	18.75	0	0.00	12	12.00		
Control Subjects	18	28.13	0	0.00	18	18.00		
Total	64	100.00	36	100.00	100	100.00		

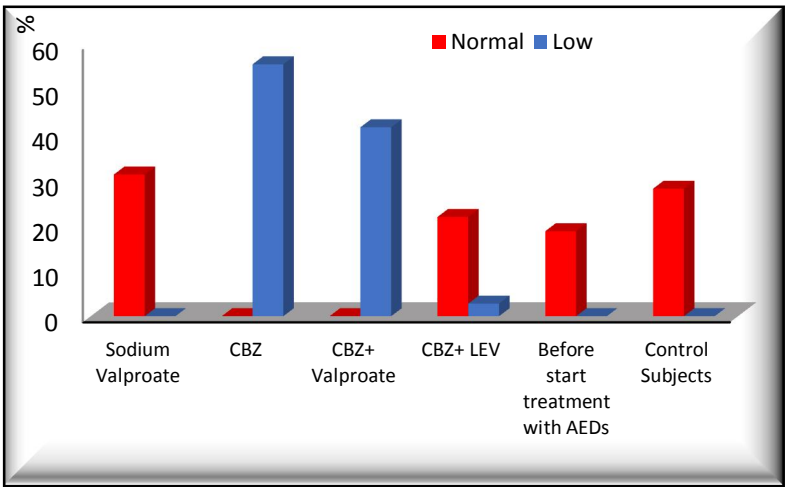

Figure (3): Figure showing Relation between serum IgM concentration, antiepileptic drugs and control subjects.

Low level of serum IgM concentrations were in patients currently on carbamazepine in monotherapy and in combination with sodium valproate [CBZ=20 (55.56%), CBZ+Valproate =15 (41.67%)].

Normal serum level IgM was found in patients currently on sodium valproate in monotherapy and in combination of carbemazepine with levetiracetam.

Normal serum level of IgM was found in patients shortly after first-presentation of one or more unprovoked epileptic seizure and before the start of treatment with any antiepileptic drugs.

4. Discussion

Adverse effects of AEDs are common, can have a considerable impact on quality of life and contribute to treatment failure in up to 40% of patients. The adverse effect profiles of AEDs differ greatly and are often a determining factor in drug selection because of the similar efficacy rates shown by most AEDs. These adverse effects are dose-dependent and reversible.

82 patients diagnosed with focal epilepsy were enrolled in this study. 12 (12%) patients presented shortly after one or more unprovoked epileptic seizures and before the start of treatment with antiepileptic drugs, the median time between first seizure and beginning of treatment was 30 days; none of these patients showed low serum level of IgG, IgA or IgM.

Low serum IgG concentrations were more common in patients treated with carbamazepine in monoterapy, combination of carbamazepine with sodium valproate and also in combination with levetiracetam.

Low serum IgM concentrations were more frequent in patients treated with carbamazepine in monotherapy and combination of carbamazepine with sodium valproate. Only one patient on Carbamazepine in combination with levetiracetam showed low serum IgM concentration.

Low serum IgA concentrations were more frequent in patients treated with carbamazepine in monotherapy, combination of carbamazepine with sodium valproate and also in combination with levetiracetam. All of our patients had an IgA deficiency, while in the reference population there were no subjects with IgA deficiency.

Although an increased risk of susceptibility to recurrent infections, especially respiratory tract infection, are the most frequently manifestations in patients with Immunoglobulin**,** none of our patients with decrement of Immunoglobulin classes had more frequent respiratory tract infection. In respect to the fact that our immunoglobulin deficient patients were asymptomatic, we did not decide to change or discontinue the drug because of its humoral effects. Therefore AED effects on Immunoglobulin can be asymptomatic without clinical significance.

Conclusion:

1. There is a significant reduction in serum level of IgG and IgA after treatment with Carbamazepine in monotherapy and in combination with sodium valproate and levetiracetam. Low serum level of IgM was detected after treatment with carbamazepine in monotherapy and in combination with valproate only.
2. Normal serum level of IgG, IgA and IgM were found after treatment with valproate.
3. Serum level of IgG, IgA and IgM is not altered in patients shortly after the first presentation with epileptic seizures and before start treatment with antiepileptic drugs.

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