Correlation Between Serum Level Of Immunoglobulin And Antiepileptic Drugs In Sample Of Egyptian Epileptic Patients

Thesis

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Contents

List of Abbreviation

ACTH	**:**	Adrenocorticotropic hormone
AMPA	**:**	Amino-3-hydroxy-5-methyl-4-isoxazole propionicacid
AED	**:**	Antiepileptic drugs
AHS	**:**	Antiepileptic hypersensitivity syndrome
ANABs	**:**	Antineuronal autoantibodies
AUC	**:**	Area under the curve
BBB	**:**	Blood brain barrier
BBBD	**:**	Blood brain barrier disruption
CBZ	**:**	carbamazepine
CNS	**:**	Central nervous system
CSF	**:**	Cereprospinal fluid
CXCL12	**:**	Chemokine receptor
CXCLR4	**:**	Chemokine receptor
CCL2	**:**	Chemokine receptor
CCR2	**:**	Chemokine receptor
CVID	**:**	Common variable immunodeficiency
CFS	**:**	Complex febrile seizure
Caspr2	**:**	Contactin-associated protein-like 2
COX-2	**:**	cyclooxygenase
CYP	**:**	Cytochrome P
CYP3A4	**:**	Cytochrome P450 3A4
DHS	**:**	Drug hypersensitivity syndrome
DRESS	**:**	Drug rash with eosinophilia and systemic symtoms
FCD	**:**	Focal cortical dysplasia
GTCs	**:**	Generalized tonic clonic seizure
HHV-6	**:**	High human herpes virus -6
HMGB 1	**:**	High mobility group box 1
HS	**:**	Hippocampal sclerosis
Hu	**:**	Hu intracellular tumor antigen
HPA	**:**	Hypothalamic-pitutary-adrenal
IHC	**:**	Immune histochemical
IG	**:**	immunoglobulin
ISH	**:**	In situ hybridization
IFN	**:**	Interferon
IL	**:**	interleukin
IL-1RA	**:**	Interleukin 1receptor antagonist
IL-1b	**:**	Interleukin-1b
IL-6	**:**	Interleukin-6
ILAE	**:**	International league against Epilepsy

IVIG	**:**	Intravenous immunoglobulin
LEMS	**:**	Lambert-Eaton myasthenic syndrome
LTG	**:**	lamotrigine
LGI1	**:**	Leucine-rich glioma- inactivated 1
LEV	**:**	levetiracetam
LPS	**:**	lipopolysaccharides
LE	**:**	Lupus erythematosus
Ma2	**:**	Ma2 intracellular tumer antigen
MTS	**:**	Mesial temporal sclerosis
mRNA	**:**	Messenger RNA
ADAM22	**:**	Metalloproteinase domain-containing protein 22
MS	**:**	Multiple sclerosis
NK	**:**	Natural killer
NMDAR	**:**	N-methyl-D-aspartate receptor
NF-KB	**:**	Nuclear factor kappa-light-chain-enhancer of activated Bcells
PCR	**:**	Polymerase chain reaction
PERM	**:**	Progressive encephalomyelitis with rigidity and myoclonus
RE	**:**	Rasmussen encephalitis
SE	**:**	Status epilepticus
SPS	**:**	Stiff-person syndrome
SAM	**:**	Sympathetic-adrenal-medullary
TLE	**:**	Temporal lobe epilepsy
TLRs	**:**	Toll-like receptors
TGF	**:**	Transforming growth factor
TNF-a	**:**	Tumer necrosis factor-a
VNS	**:**	Vagus nerve stimulation
VPA	**:**	Valproic acid
VEGF	**:**	Vascular endothelial growth factor
VGKC	**:**	Voltage-gated potassium channel

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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.

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.

Patients 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 **Conculusion:** 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

Keywords: antiepileptic drugs, humoral & cellular immunity, adverse effects, serum immunoglobulin, seizures, Focal epilepsy.

INTRODUCTION

More than 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally. Nearly 80% of people with epilepsy living in low- and middle income countries ***(Lancet, 2019)*.**

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. 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)***.

Data on the effects of antiepileptic drugs on the immune system are frequently inconsistent and sometimes conflicting because the effects of drugs cannot be separated from those of seizures, first generation drugs have been most intensively investigated than the new compounds, which may explain their predominant involvement in immune mediated reactions. The patient's genetic background, the mechanism of action and the pharmacokinetic profile of AEDs and the concurrent use of

immunosuppressant drugs may act as confounders. Valproate, carbamazepine and levetiracetam have been found to modulate the immune system activity by affecting humoral and cellular immunity ***(Aarli, 2010)***.

Carbamazepine (CBZ) was the first AEDs assumed to have an effect on the immune system. It has been associated with immune dysfunction with subnormal concentrations of all immunoglobulin. In a study started in 2013, patients were followed up after the administration of carbamazepine, a significant reduction in IgG and IgA was found ***(Svalheim et al., 2013).***

Levetiracetam (LEV) has been also associated with reversible immunoglobulin deficiency. Involvement of the immune system has been studied since the drug was first used, and accordingly affects as many as 47% of the levetiracetam treated-patients. Among the changes described are IgA and IgM deficiency ***(Svalheim et al., 2013).*** Decreased serum IgG levels have been reported in a few studies and in isolated clinical cases ***(Kim et al., 2010).***

There are also a few reports suggesting that sodium valproate (VPA) may induce low levels of IgA, IgG, and IgM, where the diagnosis of common variable immunodeficiency (CVID) has been reported. Several cases of hypogammaglobulinemia, with a phenotype similar to CVID in sodium valproate-treated patients have

been noted. This observation is interesting because sodium valproate is frequently prescribed ***(Vazzani, 2011).***

Low levels of immunoglobulin as occur in some patients following the administration of antiepileptic drugs are associated with significantly increased risks of infections, primarily respiratory tract infections of bacterial origin. Patients with IgG level below 100 mg/ dl or IgM below 20 mg/dl for prolonged period have an increased risk of recurrent and sometimes life-threatening infectious episodes. Generally, IgA deficiency appears to be better tolerated. Replenishment of IgG in patients with hypogammaglobulinemia reduces the infection risk to background if IgG levels are maintained at approximately 500 mg/dl, although higher levels may be necessary in the presences of comorbidities ***(Holmes, 2013)***

Immune system dysfunction may play role in triggering or maintaining intractable seizure. Some investigators have suggested that intractable seizure unresponsive to antiepileptic drugs may reflect occult immunoglobulin deficiency. In a previous trial study; it was found that intractable seizures have been associated with IgG subclasses deficiency. Consequently, these patients received intravenous immunoglobulin. A marked reduction in the frequency of seizures to almost complete disappearance was observed ***(Shovron, 2010)*.**

AIM OF THE WORK

We aimed to verify serum concentration of immunoglobulin; IgG, IgA and IgM in patients with focal epilepsy treated with three different antiepileptic drugs carbamazepine (CBZ), Sodium valproate (VPA) and Levetiracetam (LEV) as monotherapy and as polytherapy.

INNATE AND ADAPTIVE IMMUNITY IN HUMAN EPILEPSIES

Immune mechanisms have been discovered in several neurologic diseases, some of them associated with epilepsy. These mechanisms are not only present in epilepsies caused by infectious and central nervous system inflammatory diseases **(V*ezzani et al., 2016)*** but also in epileptic disorders not associated with a clear inflammatory pathophysiology. The exact role of the inflammatory phenomena (cause, effect, or both) is a matter of intense investigation. Rapid activation of pro-inflammatory cytokines and danger signals is observed after acute epileptogenic brain injuries or after single and recurrent seizures in both experimental and clinical settings ***(Walker et al., 2016)***.

Innate Immunity in Epileptic Disorders

There is evidence supporting that several inflammatory mediators have a specific role in temporal lobe epilepsy (TLE) or in neocortical epilepsies associated with focal malformations. Rapid activation of pro-inflammatory cytokines, such as interleukin-1b (IL-1b), interleukin-6(IL-6), and tumor necrosis factor-a (TNF-a), is observed after acute and chronic seizures in animal models of acquired epilepsies ***(Iori et al., 2016).***