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# Overview of Serum Level of Interleukin-6 and Body Mass Index in Adult Epileptic Patients

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**Abstract: Background:** Overweight/obesity is considered a common comorbidity in both children and adults with epilepsy. Seizure is a transient abnormal excessive hyper synchronous neuronal activity in the brain. It can present as a paroxysmal alteration of neurological function, disturbance of consciousness, behavioral changes, cognition, emotion, motor or sensory dysfunction.The inflammation is a biological response of the immune system that can be triggered by various factors, including pathogens, damaged cells, and toxic compounds. Inflammation is a conserved evolutionary process characterized by the activation of immune and non-immune cells that protect the host from bacteria, viruses, toxins, and infections by eliminating pathogens and promoting tissue repair and restoration The aim of the present study was to review the role of serum level of interleukin-6 and body mass index in adult epileptic patients

**Keywords:** Interleukin-6; Body Mass Index ; Obesity ; Adult ; Epileptic Patients

## Introduction

Epilepsy is a chronic disorder of the brain characterized by an enduring disposition towards recurrent unprovoked seizures and by the neurobiological , cognitive , psychological , and social consequences of this condition **(1).** Ictogenesis describes the processes of transition from the interictal state to a seizure. The processes include a preictal state, with specific clinical signs and a distinct electrophysiology which may provide opportunities to anticipate, or even prevent, seizures. **(2).**

The prevalence of epilepsy differs significantly among countries depending on the local distribution of risk and etiologic factors, the number of seizures at diagnosis and if considering only active epilepsy (active prevalence) or including also cases in remission (lifetime prevalence). The overall lifetime prevalence of epilepsy was 7.60 per 1,000 population (95% CI 6.17–9.38) and was higher in LMIC (8.75 per 1,000; 95% CI 7.23–10.59) than in High income countries (5.18 per 1,000; 95% CI 3.75–7.15). The point prevalence of active epilepsy was 6.38 per 1,000 (95% CI 5.57–7.30). The median point prevalence of active epilepsy in LMIC was 6.68 (95% CI 5.45–8.10) and in HIC was 5.49 (4.16–7.26). **(3).** In selected populations, prevalence estimates also vary and tend to be higher in individuals of certain ethnicities, people in poor health, and socially deprived subjects **(4) .**

A study conducted in Egypt in Al-Manial Island reported the lifetime prevalence of epilepsy to be 6.9/1000, prevalence of active epilepsy was 5.1/1000 people, with bimodal peaks in adolescents and the Elderly **(5).**

**Classification of seizures:**

The seizure classification was first updated in 1981,prompted by the widespread use of video EEG ,which had impacted clinical practice. At the beginning of 21st century,The ILAE saught to update the seizure classification again with minor changes**.** With the 2010 revision being an intermediate stage aiming towards a final accepted epilepsy classification (Fig. 1) **(6)**.

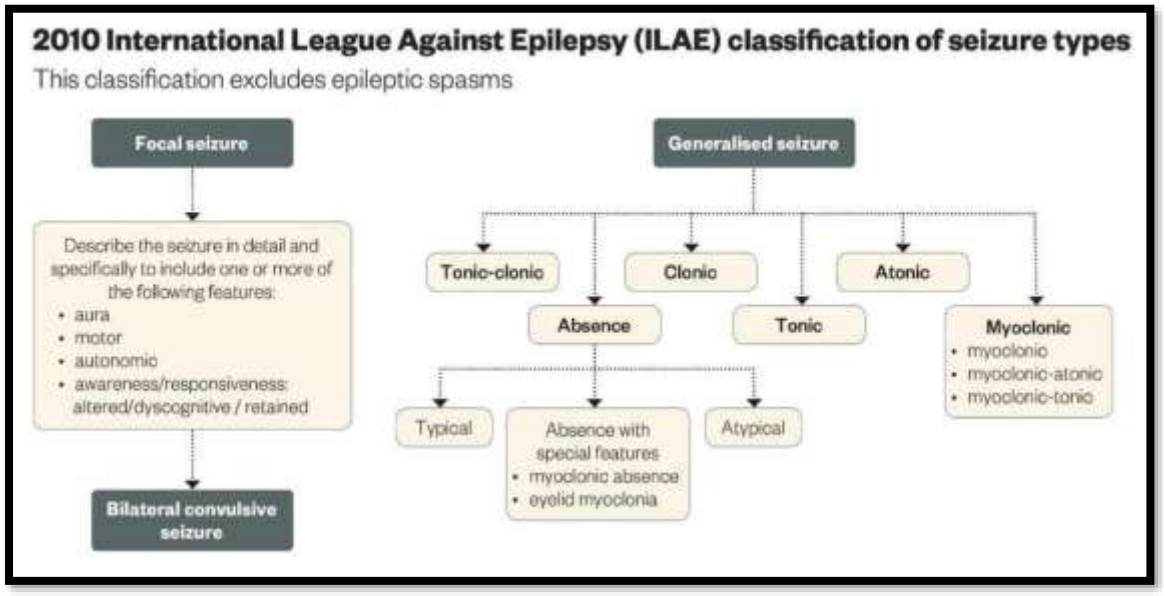


**Figure (1): ILAE seizure classification (Berg et al.,2010).**

The most recent classification of seizures and epilepsies was the ILAE 2017. The new classification is better organized with a clear elucidation of terminology and list some new seizure types. In the new classification, the clinical features of epilepsy are categorized into three levels : the seizures, the epilepsies and the epilepsy syndromes .Emphases have been made to consider etiology and comorbidities at each level **(7).**

Also , epilepsy is declared a curable disease rather than a disorder.It is said to be resolved after ten years of the seizure. Free period with the least five years spent without medication,or the patient is no longer at risk for age-related epilepsy syndrome **(8).**

**Pathophysiology:** The appearance of epileptic seizures is related to the sum of the ensuing neuronal discharges that result from prolonged bursts of action potentials, followed by neuronal hyperpolarization **(9).** Mutation in the genes encoding voltage-dependent subunits of sodium channels is leading to overactivity of the glutamatergic neurons and glutamate is released in excess or fails to be inhibited by gammaaminobutyric acid (GABA) **(10).** The brain tissue of patients with epilepsy, before or during an attack, contains elevated glutamate concentrations, especially at the epileptic focus itself. This increase may also be due to a failure in glutamate uptake, as well as glutamate-dependent changes in receptor function **(11).**

Activation of $GABA_A$ receptors leads to $Cl^-$ anions entering the neuronal cell, leading to hyperpolarization or preventing depolarization of the neuron. Several studies suggest that mutations in the α1 and γ2 subunits of

the $GABA_A$ receptor underlie the development of idiopathic epilepsy. These mutations lead to disturbances in ion permeability and receptor transport on the cell surface **(12).**

**Epileptogenesis :** is the process by which a brain network, that was previously normal, is functionally altered toward increased seizure susceptibility. Thus having an enhanced probability to generate spontaneous recurrent seizures (SRSs) **(13).** Traditionally, epileptogenesis has been considered in the context of the latent period between the epileptogenic insult and the appearance of the first clinical seizure **(14) .**

Many studies, however, have provided evidence that the frequency and severity of SRSs continue to increase after the first unprovoked or spontaneous seizure **(14)**, thus suggesting that epileptogenesis is a continuous and prolonged process. Furthermore, various forms of molecular and cellular plasticity, which are proposed to lead to the occurrence of the first unprovoked seizure, also continue indefinitely beyond the initial one, and, thus, may contribute to the progression of the epileptic condition **(15).**

The exact mechanism for epilepsy is unknown, **(16)** but a little is known about its cellular and network mechanisms. However, it is unknown under which circumstances the brain shifts into the activity of a seizure with its excessive synchronization **(17).** Changes in MicroRNAs (miRNAs) levels seems to play a leading role. MicroRNAs (miRNAs) are a family of small non-coding RNAs that control the expression levels of multiple proteins by decreasing mRNA stability and translation, and could therefore be key regulatory mechanisms and therapeutic targets in epilepsy **(18).**

**Treatment:**

**Medical treatment:**The mainstay treatment of epilepsy is anticonvulsant medications, possibly for the person's entire life. The choice of anticonvulsant is based on seizure type, epilepsy syndrome, other medications used, other health problems, and the person's age , sex and lifestyle **(19).**A single medication is recommended initially. If this is not effective, adding to a single other medication is recommended. Two medications at once is only recommended if a single medication does not work. In about half of patients, the first agent is effective; a second single agent helps in about 13% and a third or two agents at the same time may help an additional 4%. About 30% of patients continue to have seizures despite AEDs therapy **(20).**Further medications trials of AEDs in mono- or poly-therapy can be of benefit in individuals with epilepsy. It is important to review past treatment trials with the patient to assess whether the dose or frequency of dosing was adequate **(21).**The appropriateness of past AED trials to the individual's seizure-type should also be specifically evaluated, as should compliance and any potential barriers to compliance. Using a previously minimally effective AED in combination with another AED of a different mechanism of action, may maximize the effect of the currently used drug. Some suggest that drug combinations employing AEDs with different mechanisms of action may be fruitful; although neither of these approaches has been systematically evaluated **(22).**

**Surgery:** Epilepsy surgery has increasingly become a suitable therapeutic option. Indeed, three randomized controlled clinical trials in adults and one in children and several meta-analyses and systematic reviews have demonstrated its safety and efficacy in well-selected people with epilepsy **(23).** Moreover, advances in structural and functional neuroimaging and EEG video-monitoring, together with the simplification of invasive electrode implantation techniques and the advent of new neurosurgical tools, have broadened the indications for surgery, while making it both safer and less invasive. Nevertheless, surgery remains an underutilized resource **(24).** Patients with concordant abnormalities in one temporal lobe on MRI and EEG have a rate of seizure remission as high as 90 percent. Patients with nonlesional temporal lobe epilepsy also have a high

remission rate with surgical therapy. The efficacy is highest in patients in whom EEG and another imaging modality (eg, SPECT, PET, or MRS) reveal a consistent location of the epileptic focus **(25).**

**Vagus nerve stimulation:**Vagus nerve stimulation was approved by the United States Food and Drug Administration in 1997 and subsequently has been adopted in more than 70 countries for a wide array of medically intractable seizures including localization-related epilepsy (with multiple or unresectable foci), after unsuccessful intracranial epilepsy operations, and in generalized epilepsy syndromes **(26).**

**Ketogenic diet:** The classic ketogenic diet (CKD) consists of a high-fat and low-protein and carbohydrate diet, with restricted calories and fluids. The diet mimics the fasting state, altering the metabolism to use fats as a primary fuel source; catabolism of fatty acids in the liver produces ketone bodies (KB), which induces urinary ketosis **(27).** Recent studies have found a significantly positive outcome with the use of the KD for treatment of refractory epilepsy in children and adults **( 28).** The first documented modern use of fasting for epilepsy appeared in 1911, when fasting successfully improved the seizures of 20 children and adults with epilepsy **(29).** Subsequently, it was discovered that the benefits of fasting could be replicated by inducing ketosis through a high-fat diet, which led to implementation of a KD in epilepsy patients, with the distinct advantage that this treatment could be maintained for a prolonged period of time **(29).** Despite a steady increase over the past decade in our knowledge of the underlying mechanisms of the KD, it is still not completely understood how the diet is clinically effective in seizure disorders **(*29*).** A recent meta-analysis showed that 53% of patients with intractable epilepsy can achieve a reduction in seizure frequency of > 50% with a ketogenic diet **(30) .**

**Epidemiologic studies define obesity using the body mass index**

The main factors that may be changed by epilepsy in these brain areas are leptin (as a satiety hormone), ghrelin (as a hunger hormone), and adiponectin (as a starvation hormone) **(31).**

The other factor that may contribute to the association between epilepsy and body weight is environment and lifestyle. Lack of enough physical activity and bad dietary habits may increase the prevalence of obesity in PWE **(32).**

Finally, AEDs may also affect body weight. This effect is not the same for all AEDs; some of them may lead to weight gain, some may cause weight loss, and others do not have any effect on the body weight . Valproic acid, gabapentin, pregabaline, perampanel, vigabatrin, and carbamazepine may increase body weight. Whereas, topiramate, rufinamide, cannabidiol, zonisamide, and felbamate may cause weight loss. Some of AEDs are weight neutral, including lamotrigine, lacosamide, eslicarbazepine, levetiracetam, and phenytoin **(33).**

**Antiepileptic drugs as (threat) modifiers to lipid metabolism:**

Most AEDs, especially old-generation drugs such as phenytoin, carbamazepine, and phenobarbital, are enzyme inducers and thus have adverse effects on various metabolic and biochemical processes of the body . **(34).** Long-term administration of these drugs can result in enhancement of total cholesterol, low density lipoprotein (LDL)-cholesterol, and even high density lipoprotein (HDL)-cholesterol as a consequence of stimulation of endogenous hepatic synthesis of cholesterol **(34).**

Lipid abnormalities have also been reported in children, who received phenytoin as monotherapy for 6 months and beyond **(35).** Also, HDL reduction and triglyceride increase following valproate have been reported **(36).** Similarly, the raise in LDL has been reported following oxcarbazepine and topiramate **(37).** While eslicarbazepine acetate may positively affect lipid metabolism profile in patients with epilepsy, in vivo studies

suggest that eslicarbazepine acetate can induce CYP3A4, decreasing plasma concentrations of drugs that are metabolized by this isoenzyme (e.g., simvastatin). Patients receiving enzyme-inducing drugs are significantly more likely to require multiple upward dose adjustments of their statin medication **(38).**

**Neuroinflammation in Epilepsy Pathophysiology :**

Neuroinflammation, either due to brain damage or systemic inflammation, alters the messaging pathways within the brain and affects all the cells in the CNS, including neurons and glial cells. The unbalanced mediators and increased inflammatory molecules give rise to neuronal hyperexcitability making the brain prone to ictogenesis and epileptogenesis **(39).**

An accumulating body of evidence has highlighted that TLR4 activation may induce seizures. High-mobility group box 1 (HMGB1), a DNA-binding protein , in physiologic states, it exists at low levels in the brain, but in pathological and inflammatory conditions, it can be secreted from damaged cells as a damageassociated molecular pattern (DAMP) **(40).** It is demonstrated that HMGB1 may be secreted from neurons, glial cells, and endothelial cells under an inflammatory state or when stimulated by hypoxia or seizures. The increase in the adenosine triphosphate (ATP) in the brain triggers the release of HMGB1**(41).**

**IL-6 and epileptogenesis :**

IL-6 has been generally categorized as a pro inflammatory cytokines with key roles in ictogenesis and epilepsy, albeit it could also exert some anti-inflammatory effects **(39).** Human IL-6 is made up of 212 amino acids including a 28-amino acidsignal peptide, and its gene has been mapped to chromosome 7p21. The IL-6 receptor -signaling system is made up of two receptor chains and downstream signaling molecules **(42).** The IL-6 receptor (IL-6) constitutes the IL-6 binding chain which occurs in two forms , 80 kilodalton (KDa) Transmembrane and 50-55 kDa soluble IL-6R(sIL-6R),where 130 KDa glycoprotein 130 (gp130) constitutes the signal-transducing chain **(43).**

The molecular mechanism of IL6 signaling is mediated by IL6 receptor α (IL6-Rα) through the signaling protein IL6ST (also known as gp130). Canonical IL6 signaling involves binding of IL6 to an IL6Rα/IL6ST complex at the plasma membrane **(44).**

Nevertheless, most studies have highlighted that the excessive amount of IL-6 in the brain is associated with different neurological disorders such as Multiple Sclerosis , Parkinson's disease , and Alzheimer's disease , and it has proconvulsive effects in epilepsy **(45).**

Considering the strong evidence linking IL-6 to pathophysiology, clinical expression, and treatment response in epilepsy, we hypothesized that a treatment that blocks or reduces this proinflammatory cytokine production and/or action could have a therapeutic effect in absence seizures. IL-6 blockade is a current therapeutic strategy for autoimmune/inflammatory conditions **(46).**

Interleukin 6 (IL6) has many physiological actions that regulate metabolism **(47).** Similarly, IL6 signaling by hepatocytes causes increased tolerance to both glucose and insulin **(48).** Moreover, IL6 acts on adipose tissue to increase leptin secretion and suppress satiety **(49).**

Furthermore, IL6 signaling in the paraventricular nucleus of the hypothalamus improves energy and glucose homeostasis in response to obesity **(50).** It has also established that IL6 can increase insulin secretion by an incretin-based mechanism **(51).**

Interleukin 6 is therefore a potent cytokine that acts at key sites of metabolic regulation in multiple tissues. **(52).** Interleukin 6 therefore targets multiple physiological processes that impact whole-body metabolism **(53)**

Previous study shows that weight loss does improve inflammation in terms of a number of obesity related inflammatory markers (ORIM), specifically characterized by a decrease in the inflammatory markers (CRP, TNF-α, IL-6 and leptin) and an increase in the anti-inflammatory marker, adiponectin. Moreover, the greatest and more consistent improvements are noted in those studies achieving at least a 10 % weight loss. A systematic review quantified that a 1 kg weight loss will produce a − 0·13 mg/l change in CRP through diet and lifestyle modifications, which is increased to a − 0·16 mg/l change per 1 kg loss of body weight induced by gastric surgery. **(54).**

Caloric restriction causes changes on gene expression of cytokines reducing the IL-6 mRNA and IL-1B expression and improving insulin sensitivity **(55)** and regulates gene expression in adipose tissue increasing mitochondrial function **(56).**

**Conclusion:**

The mean serum IL-6 and oxidative stress levels in refractory epilepsy patients were higher and the serum adiponectin level was lower than the healthy control group. These findings may be associated with an increased risk of seizures, atherosclerosis and cardiovascular disease in refractory epilepsy patients.

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