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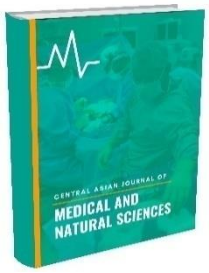

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Genotype of IL-1β Gene in Epilepsy Patients

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Abstract: Background; Epilepsy is caused by hyper excitability and an imbalance between excitation and inhibition, which results in seizures. Epilepsy is a highly common neurological disorder on a global scale, impacting approximately 50 million individuals as stated by the World Health Organization (WHO). It is identified as a neurological condition marked by repetitive seizures triggered by sudden surges in electrical activity within the brain. These seizures arise from abnormal discharges of neurons or the synchronized hyper excitability of neurons. However, various people experience these seizures at different rates. Based on the etiology, epilepsy is categorized into three categories: acquired, idiopathic, and epilepsy of genetic or developmental origin. The onset of idiopathic epilepsy starts in childhood, and it lacks any neurological symptoms. Idiopathic epilepsies include juvenile myoclonic epilepsy and childhood absence epilepsy, among others. Acquired epilepsy is linked to observable structural abnormalities in the brain. The causes of acquired epilepsy encompass various factors that occur during prenatal and infantile stages, cerebral trauma, tumors, infections, hippocampal sclerosis, cerebrovascular disorders, and disorders of the cerebral immune system. For instance, specific examples include viral meningitis, meningioma, cavernous hemangioma, cerebral infarction, and epilepsy triggered by open head surgery. The cause of cryptogenic epilepsy is uncertain. It can be challenging to determine the etiology among acute and distant factors. The 7.5 kb IL-1 gene has a distinct TATA box in its proximal promoter region 1, seven exons, and six introns. It is controlled by distal and proximal promoter elements. IL-1 is expressed as a 31-kDa inactive precursor, as is the case with the majority of the cytokines within the IL-1 family, mostly in response to inflammatory stimuli. A microbial product may serve as the stimulus, although cytokines

including tumor necrosis factor (TNF), IL-18, IL-1, and even IL-1 itself can trigger IL-1 transcription. Contrary to IL-1, which is present constitutively in healthy cells, IL-1 must first undergo a sequence of intracellular events before it may cause inflammation. Only a small subset of cell types, including tissue macrophages, blood monocytes, and dendritic cells.

Methodology: The study comprised 90 patients (51 male, 39 female) 50 epilepsy patient and 40 control, the patient and control who attended in Basra Teaching Hospital between November-2022 to March-2023 in Basrah, Southern Iraq. Apparently healthy people age range 2 to 62 years were considered as control groups in this study. IL-1b is examination by molecular processes (Nested PCR). This work was carried out at the College of Health and Medical Techniques' molecular biology laboratory.

Results: From the data provided, we can see that there is a difference in the AA, GG and GA genotypes between the patient group and the control group, this difference is represented by the p-value calculated as 0.0001. Also there is a statistically significant difference in genotype frequencies between the focal and generalized epilepsy.

Conclusions: In conclusion, interleukin-1 beta (IL-1β) appears to be involved in the pathogenesis of epilepsy, particularly in the context of genetic susceptibility.

Key words: epilepsy, IL-1β, genotyping.

Introduction

Epilepsy is caused by hyper excitability and an imbalance between excitation and inhibition, which results in seizures (Giourou et al., 2015). Epilepsy is one of the most prevalent neurological illnesses worldwide, affecting around 50 million people, according to the WHO (Stafstrom & Carmant, 2015).

Based on the etiology, epilepsy is categorized into three categories: acquired, idiopathic, and epilepsy of genetic or developmental origin. The onset of idiopathic epilepsy starts in childhood, and it lacks any neurological symptoms. Idiopathic epilepsies include juvenile myoclonic epilepsy and childhood absence epilepsy, among others (Fisher *et al.*, 2017).

Acquired epilepsy is linked to observable structural abnormalities in the brain. The causes of acquired epilepsy encompass various factors that occur during prenatal and infantile stages, cerebral trauma, tumors, infections, hippocampal sclerosis, cerebrovascular disorders, and disorders of the cerebral immune system. For instance, specific examples include viral meningitis, meningioma, cavernous hemangioma, cerebral infarction, and epilepsy triggered by open head surgery. The cause of cryptogenic epilepsy is uncertain. It can be challenging to determine the etiology among acute and distant factors (Valton *et al.*, 2020).

The International League Against Epilepsy (ILAE), 2017, which was published in March 2017, provided the most recent classification of epilepsies. This updated classification includes a list of new seizure types, is better organized, and clarifies terminology. Since different medications are typically beneficial for various seizure types, classification and grouping into related entities can improve epilepsy diagnosis and management (Valton *et al.*, 2020).

Seizures, epilepsies, and epilepsy syndromes are the three categories used by the ILAE to classify the clinical characteristics of epilepsy. At each stage, emphasis has been placed on taking the etiology and comorbidities into account. Moreover, epilepsy is classified as a disease rather than a disorder and is treatable (Lüders *et al.*, 2019).

Genetics appears to play a significant role in the etiology of epilepsy, a frequent episodic neurological ailment or condition marked by recurring epileptic seizures. Early linkage studies have identified a number of loci that might include epilepsy susceptibility genes, and mutational analysis has found a number of mutations in both ion channel and non ion channel genes in patients with idiopathic epilepsy (Myers *et al.*, 2019). Numerous genes linked to monogenic forms of epilepsy have been discovered through recent genetic research (Yelnik *et al.*, 2016).

The existence of various types of linked neuronal autoantibodies plays a major role in the definition of AE, and our current understanding of the related clinical manifestations has evolved over time (Lapalme-Remis and Nguyen, 2022).

Although the exact etiology of autoimmunity is often unknown, some patients may have an underlying malignancy that triggers a paraneoplastic immune response (Yavuz *et al.*, 2022). Also, the concept of immune-mediated epileptogenesis may drive new therapy trials that concentrate on the main reason for seizure development and provide patients with new treatment options (Aguilar-Castillo *et al.*, 2022).

Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine that has been implicated in various neurological disorders, including epilepsy. Several studies have investigated the role of IL-1β in the genetic aspects of epilepsy.

Epilepsy is a complex neurological disorder characterized by recurrent seizures. While the exact mechanisms underlying epilepsy are not fully understood, emerging evidence suggests that inflammation plays a crucial role in the pathogenesis of seizures. Inflammatory cytokines, such as IL-1β, have been identified as key mediators of neuroinflammation in epilepsy. IL-1β is primarily produced by activated microglia and astrocytes in the brain in response to various stimuli, including infection, injury, and inflammation. Elevated levels of IL-1β have been observed in animal models and human studies of epilepsy, suggesting its involvement in the epileptogenic process. Genetic studies have provided valuable insights into the role of IL-1β in epilepsy (Vezzani *et al.*, 2016).

Methodology

Case-control study was conducted from November-2022 to March-2023 on 90 patients (51 male, 39 female) 50 epilepsy patient and 40 control, the patients included 24 drug resistant and 26 responders aged 2-60 years old, who attended in Basra Teaching Hospital. Apparently healthy people age range 2 to 62 years were considered as control groups in this study in Basrah, Southern Iraq. We Patients with other autoimmune disease, smoking patients, patients who take immune drugs, stroke excluded from participating in the study. Blood samples for the measurement of serum IL-1b, a total of 5 ml of blood was drawn from each patient and control subject were placed in EDTA-k2 was used for DNA extraction by use PCR and gel tubes and allowed to coagulate at room temperature for 30 minutes before being centrifuged for 15 minutes at a speed of 3000 rpm to separate the components. The serum should be separated and kept at a temperature of -20 degrees Celsius until use.

Statistical Analysis

The statistically significant differences were determined using SPSS (version 26).

Results

From the data provided in table (1), we can see that there is a difference in the AA, GG and GA genotypes between the patient group and the control group. This difference is represented by the p-value calculated as 0.0001.

Table (1): Associations of genotype with category of the study individuals

		Category		P-value*
		Patient	Control	
Genotype	AA	7	0	0.0001
		14.0%	0.0%	
	GG	22	40	
		44.0%	100.0%	
	GA	21	0	
		42.0%	0.0%	
Total		50	40	
		100.0%	100.0%	

* Fisher's Exact Test

Table (2) show the p-value for comparing the genotype distribution between males and females is (0.611), indicating that there is no statistically significant difference in genotype frequencies between the two groups

Table (2): Sex Genotype

Sex * Genotype		Genotype			Total	P-value
		AA	GG	GA		
Sex	Male	5	35	14	54	0.611
		71.4%	56.5%	66.7%	60.0%	
	Female	2	27	7	36	
		28.6%	43.5%	33.3%	40.0%	
Total		7	62	21	90	
		100.0%	100.0%	100.0%	100.0%	

* Fisher's Exact Test

The p-value for comparing the genotype distribution between the focal and generalized epilepsy groups is 0.001, indicating a statistically significant difference in genotype frequencies between the two group as show in table (3).

Table (3): Type of Epilepsy Genotype

		Genotype			Total	P-value
		AA	GG	GA		
Type of Epilepsy	Focal	3	22	18	43	0.001
		42.9%	100.0%	85.7%	86.0%	
	Generalized	4	0	3	7	
		57.1%	0.0%	14.3%	14.0%	

Total	7	22	21	50	
	100.0%	100.0%	100.0%	100.0%	

* Fisher's Exact Test

Based on the data provided in table (4), the distribution of genotypes (AA, GG, GA) for drug resistance, the p-value for comparing the genotype distribution between drug resistance and no drug resistance is 0.928, indicating no statistically significant difference in genotype frequencies between the two groups.

Table (4): Drug resistance * Genotype

		Genotype			Total	P-value
		AA	GG	GA		
Drug resistance	Yes	4	10	10	24	0.928
		57.1%	45.5%	47.6%	48.0%	
	No	3	12	11	26	
		42.9%	54.5%	52.4%	52.0%	
Total		7	22	21	50	
		100.0%	100.0%	100.0%	100.0%	

* Fisher's Exact Test

The p-value for comparing the genotype distribution among different age groups is 0.009, indicating a statistically significant difference in genotype frequencies among the age groups as show in table (5).

Table (5): Age group (Year) * Genotype

		Genotype			Total	P-value
		AA	GG	GA		
Age group (Year)	≤15	6	8	13	27	0.009
		85.7%	36.4%	61.9%	54.0%	
	16 - 25	0	5	4	9	
		0.0%	22.7%	19.0%	18.0%	
	26 - 35	0	7	0	7	
		0.0%	31.8%	0.0%	14.0%	
	36 - 45	0	0	2	2	
		0.0%	0.0%	9.5%	4.0%	
	46 - 55	0	2	0	2	
		0.0%	9.1%	0.0%	4.0%	
	≥56	1	0	2	3	
		14.3%	0.0%	9.5%	6.0%	
Total		7	22	21	50	
		100.0%	100.0%	100.0%	100.0%	

* Fisher's Exact Test

Discussion

Genetic studies have provided valuable insights into the role of IL-1β in epilepsy. Several genetic variations within the IL-1β gene and its receptor gene (IL1R1) have been investigated for their association with epilepsy susceptibility and disease progression. For example, single nucleotide polymorphisms (SNPs) in the IL-1β gene, such as rs16944 and rs1143627, have been studied in relation to epilepsy risk and seizure severity.

In the current study and from the data provided, more frequencies are GG of IL-1β in patients and control (44.0% and100.0% respectively) and there is a difference statistical in the AA, GG and GA genotypes between the patient group and the control group. This difference is represented by the p-value calculated as 0.0001, this results supported with study of Kumari et al. that showed that the Frequencies of GA (48.9%)c (50.1%)p), GG ((30.5%)c and (14.6%)p) and AA 1 (20.5%)c and (35.3%)p) genotypes were found to be significantly higher in epilepsy patients versus control (Kumari et al., 2013) .other study of Shibata et al showed that there were difference between the AESD group and the control group in terms of the ratio of individuals who were higher producers of IL-1β. In AESD, the ratio of individuals with the TT genotype was significantly lower compared to the controls (Shibata *et al.*, 2022).

In our study the p-value for comparing the genotype distribution between males and females is (0.611), indicating that there is no statistically significant difference in genotype frequencies between the two groups while there is statistically significant difference in genotype frequencies among age groups (p =0.009) the study of Abe et al agree with the first (sex) and dis agree with other (age groups) it's said that there is no statistically significant difference in genotype frequencies between gender group and also age groups (p = 0.50 and p=0.73 respectively) (Abe et al., 2008).

In the present study the p-value for comparing the genotype distribution between the focal and generalized epilepsy groups is 0.001, indicating a statistically significant difference in genotype frequencies between the two group and Based on the data provided, the distribution of genotypes (AA, GG, GA) for drug resistance, The p-value for comparing the genotype distribution between drug resistance and no drug resistance is(p= 0.928), indicating no statistically significant difference in genotype frequencies between the two groups, the study of Mantegazza et al. showed that In the study, it was observed that the frequencies of GA genotypes (comprising 53.2% of variant c and 55.1% of variant p), GG genotypes (comprising 15.3% of variant c and 10.1% of variant p), and AA genotypes (comprising 31.4% of variant c and 34.8% of variant p) in drugs resistance were significantly in epilepsy patients compared to the control group (Mantegazza *et al*., 2010). Other study of Naimo et al revealed that among patients with idiopathic epilepsy or those without associated complications like mental retardation, the frequency of the AA genotype was found to be higher in individual's resistant to carbamazepine (CBZ) treatment. This discovery supports the hypothesis that the development of CBZ-resistant epilepsy may be attributed to a diminished sensitivity of sodium channels to the drug (Naimo *et al.*, 2019).

A study by Sallam and colleagues (2019) conducted a meta-analysis of genetic studies and found a significant association between the IL1β rs16944 polymorphism and increased risk of epilepsy (Sallam *et al.*,2019). Another study by Fan et al. (2019) investigated the association of IL-1β gene variations with mesial temporal lobe epilepsy (MTLE) in a Chinese population, and they identified a significant association between the IL1β rs16944 polymorphism and MTLE susceptibility (Fan *et al*.,2019).

Moreover, animal models have provided further evidence for the involvement of IL-1β in epilepsy. Studies using IL-1β knockout mice have shown a reduced susceptibility to seizures and improved seizure outcomes compared to wild-type mice. These findings suggest that IL-1β may play a crucial role in the development and progression of epilepsy.

It is important to note that the exact mechanisms through which IL-1β contributes to epilepsy are still under investigation. IL-1β can promote neuronal excitability, disrupt the blood-brain barrier, and enhance synaptic transmission, all of which may contribute to seizure generation and progression.

Conclusion

In conclusion, interleukin-1 beta (IL-1β) appears to be involved in the pathogenesis of epilepsy, particularly in the context of genetic susceptibility. Genetic variations within the IL-1β gene have been

associated with increased epilepsy risk, and animal studies support the role of IL-1β in seizure generation. Further research is needed to elucidate the specific mechanisms by which IL-1β contributes to epilepsy and to explore potential therapeutic targets

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