

**Study of inflammatory markers in seizure disorder****Raushan Kumar<sup>1\*</sup>, Ashiti Jain<sup>2</sup>, Jaishree Ghanekar<sup>3</sup>**<sup>1</sup>*PG Resident, MGM Hospital, Kamothe / Medicine Department, Navi Mumbai, Maharashtra, India*<sup>2</sup>*Senior Resident, MGM Hospital, Kamothe / Medicine Department, Navi Mumbai, Maharashtra, India*<sup>3</sup>*Professor and HOD, Department Of General Medicine, MGM Hospital, Kamothe / Medicine Department, Navi Mumbai, Maharashtra, India*

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**Abstract**

**Background:** Over the past 10 years an increasing body of clinical and experimental evidence has provided strong support to the hypothesis that inflammatory processes within the brain might constitute a common and crucial mechanism in the pathophysiology of seizures and epilepsy. **Objective:** The study aimed to focus on various markers for inflammation in seizure like WBC, elevated BT, HSCRP along with serum ferritin and ESR. **Methodology:** A tertiary care hospital based prospective, observational and comparative study was conducted to study the inflammatory markers in seizures on 100 patients – 50 patients each of first episode of seizure and known case of seizure, who reported to the Department of General medicine (OPD, MMW and FMW), Geriatric medicine (MMW and FMW), Neurology (OPD) and Emergency medicine (ER) at Mahatma Gandhi Mission Medical college, Navi Mumbai. **Result:** Most of the study population who presented with 1st episode of seizure belonged to the age up to 25 years (26%) and 26 to 35 years (22%) while most of the study population who were known case of seizure disorder belonged to the younger age group of less than and equal to 25 years (36%). ESR was increased in 18% of cases with 1<sup>st</sup> episode of seizure and 16% of known case of seizure. It was most commonly increased in Drug Default Seizure (19.4%) followed by CNS Infections (16.1 %). Raised ESR levels were most commonly associated with generalized tonic clonic seizures. Serum Ferritin was equally increased in both cases with 1st episode of seizure (4%) and known case of seizure (4%). It was increased most commonly in CNS Infections (17.2 %) followed by Drug Default Seizure (16.1%), Post stroke seizure (15.1%), Alcohol withdrawal seizure (15.1%) and Scar Epilepsy (7.52%). Increased levels of ferritin was most commonly observed in Generalized tonic clonic seizure (76.3%) followed by complex partial seizure (10.8%). **Conclusion:** Inflammatory markers except ESR and FERRITIN, WBC and HSCRP were increased most commonly in GTCS. Markers of inflammation evaluated in the present study cannot not be used as diagnostic markers for different type of seizures since their correlation did not reach the statistically significant value. Study reported significant increase in HSCRP levels in GTCS (64%). It is observed that WBC levels were increased in 34% of cases with 1<sup>st</sup> episode of seizure and 50% of known case of seizure

**Keywords:** Inflammatory markers & Seizure disorder.

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**Introduction**

Epilepsy is estimated by the World Health Organization to affect 0.8% of the world's population. In recent years, an increasing body of evidence has indicated that there is a complex relationship between

epilepsy and the immune system[1]. Over the past 10 years an increasing body of clinical and experimental evidence has provided strong support to the hypothesis that inflammatory processes within the brain might constitute a common and crucial mechanism in the pathophysiology of seizures and epilepsy[2-5]. The first insights into the potential role of inflammation in human epilepsy were derived from clinical evidence indicating that steroids and other anti-inflammatory treatments displayed anticonvulsant activity in some drug-resistant epilepsies[1-3]. Additional evidence came from febrile seizures, which always coincide with

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and are often caused by a rise in the levels of pro-inflammatory agents[1,2]. This study focuses on an inflammation-like response (I response), including elevated BT, white blood cell (WBC) count, high sensitive C-reactive protein (HSCRP) levels, along with acute phase reactants i.e. sr. ferritin levels, ESR associated with acute seizures[1].

### Objective

- To study the biomarkers of inflammation in seizures.

### Methods

A tertiary care hospital based prospective, observational and comparative study was conducted to study the inflammatory markers in seizures on 100 patients – 50 patients each of first episode of seizure and known case of seizure, who reported to the department of General medicine (OPD, MMW and FMW), Geriatric medicine (MMW and FMW), Neurology (OPD) and Emergency medicine (ER) at Mahatma Gandhi Mission Medical college, Navi Mumbai.

### Inclusion criteria

- Age group- 15-65 year.
- Sex- both males and females.
- All patients who presented with acute seizures (including those with first episode of seizure reporting to hospital within 24hrs as well as known case of seizure disorder).
- All patients who presented with seizures post head trauma.
- All patients who presented with seizure co-existing with stroke.
- All patients who underwent a diagnostic brain magnetic resonance imaging (MRI) examination on a 1.5 Tesla machine (General Electric Signa HD, Milwaukee, WI, U.S.A.), EEG were included[6-8].

### Exclusion criteria

- Age <15y and > 65yr
- Patients with positive fever profile (malaria, dengue, typhoid, leptospirosis), positive culture(blood, urine) reports

- All those conditions where hsCRP, serum ferritin and ESR were raised.
- Patients with Cardiovascular diseases including recent myocardial infarction, rheumatic fever, infective endocarditis.
- Patients with peripheral vascular disease.
- Patients with renal diseases including ESRD, RCC, CKD on haemodialysis.
- Patients with acute on chronic liver infections, chronic liver disease.
- Patients with anaemia (with / without iron deficiency anaemia), leukaemia, lymphoma.
- Patients with malignancies.
- Patients with systemic diseases including systemic lupus erythematosus, rheumatoid arthritis, giant cell arteritis, polymyalgia rheumatica.
- Patients with skin infections –erysipelas.
- Patients who underwent any surgery recently.
- Patients with chronic diseases like tuberculosis, thyroid disease (hyperthyroidism).
- Pregnant females, females taking oral contraceptive pills.
- Patients with osteomyelitis
- Patients with neurodegenerative diseases- dementia, Alzheimer's disease[9-11].

### Investigations

Leucocytosis was considered for a WBC count above 11,000 cells/mm<sup>3</sup>. TLC was measured by XP-100/XN-1000 haematology analyser fully automated on venous samples collected in EDTA vacutainers.

HsCRP, ESR were measured by the fully automated AU480 biochemistry analyser on venous samples collected in plain vacutainers from 50 patients of acute seizure disorder and 50 patients of known case of seizure disorder.

hsCRP values cut off was set as:

**Table 1: hsCRP values cut off**

Less than 1.0 mg/L	low
1.0	3.0 mg/L
3.1	9.9 mg/L
Greater than 9.9 mg/L	very high

Westergren's method was used for measurement of ESR. The reference range for erythrocyte sedimentation rate taken into consideration was[1]:

### Adults (Westergren method)

- Men under 50 years old: < 15 mm/hr
- Men over 50 years old: < 20 mm/hr
- Women under 50 years old: < 20 mm/hr

•Women over 50 years old: < 30 mm/hr  
 Serum ferritin levels were measured by Access 2 by Beckman coulter.  
 The reference range of ferritin was taken as:  
 •Males: 23-336 ng/mL  
 •Females: 11-306 ng/mL

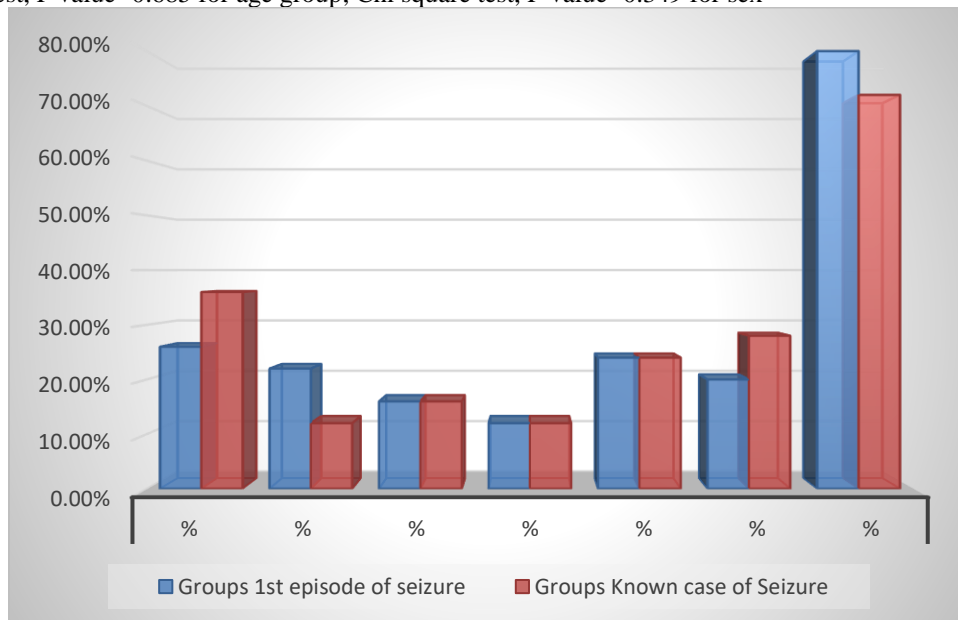
**Statistical Analysis**

Observations were considered valid only if the specimens were analysed within 2 hour from venesection, to avoid the problems occurring when EDTA collected samples are analysed.

**Table 2:Demographic Profile (N = 100)**

			Groups		Total
			1st episode of seizure	Known case of Seizure	
Age	Up to 25 years	Count	13	18	31
		%	26.00%	36.00%	31.00%
	26 to 35 years	Count	11	6	17
		%	22.00%	12.00%	17.00%
	36 to 45 years	Count	8	8	16
		%	16.00%	16.00%	16.00%
	46 to 55 years	Count	6	6	12
		%	12.00%	12.00%	12.00%
	more than 55 years	Count	12	12	24
		%	24.00%	24.00%	24.00%
Sex	Female	Count	10	14	24
		%	20.00%	28.00%	24.00%
	Male	Count	40	36	76
		%	80.00%	72.00%	76.00%
Total	Count	50	50	100	
	%	100.00%	100.00%	100.00%	

Chi square test, P value- 0.685 for age group; Chi square test, P value- 0.349 for sex



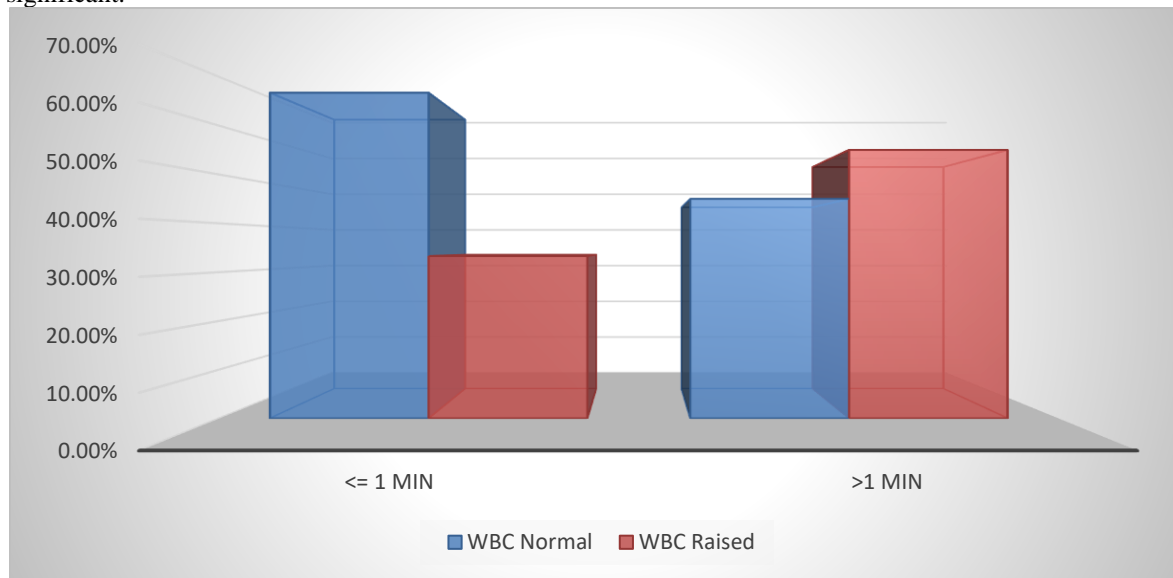
**Fig 1: Demographic Profile (N=100)**

**Table 3:Duration Of Seizure Vs WBC (N = 100)**

			WBC		Total
			Normal	Raised	
Duration Of Seizure	<= 1 MIN	Count	40	20	60
		%	66.7%	33.3%	100.0%
	>1 MIN	Count	18	22	40
		%	45.0%	55.0%	100.0%
Total		Count	58	42	100
		%	58.0%	42.0%	100.0%

Chi square test, P value- 0.032

As seen in the above table, WBC was normal in 45% of cases with more than 1 minute of duration of seizure while it was increased in 55% of cases with more than 1 minute of duration of seizure and the difference was statistically significant.



**Fig 2: Duration of seizure vs WBC (N = 100)**

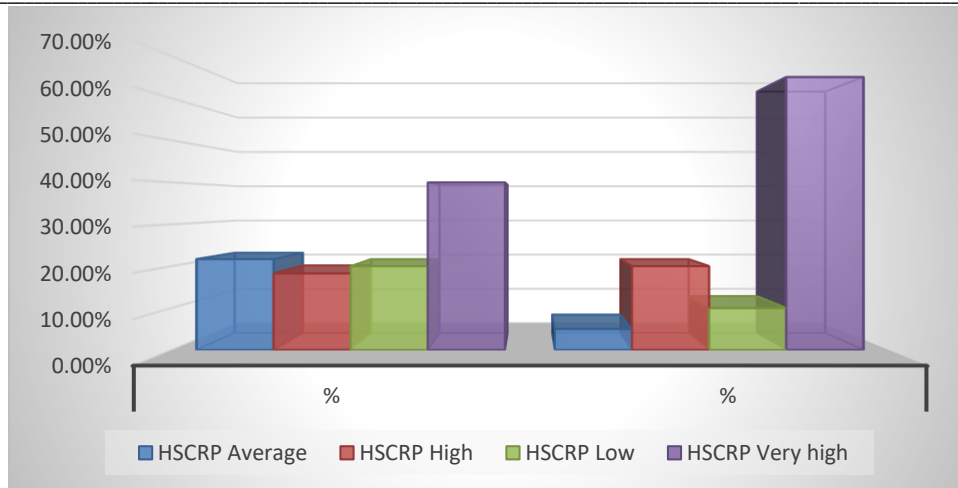
**Table 4: Duration of seizure VS HSCR P (N = 100)**

			HSCR P				Total
			Average	High	Low	Very high	
Duration of Seizure	<= 1 MIN	Count	13	11	12	24	60
		%	21.7%	18.3%	20.0%	40.0%	100.0%
	>1 MIN	Count	2	8	4	26	40
		%	5.0%	20.0%	10.0%	65.0%	100.0%
Total		Count	15	19	16	50	100
		%	15.0%	19.0%	16.0%	50.0%	100.0%

Chi square test, P value- 0.030

As seen in the above table, among the cases with seizure persisting for more than 1 minute of duration, most of the study population had very high levels of

HSCR P (65% ) followed by high (20% ) and low (10% ) and the difference was statistically significant.



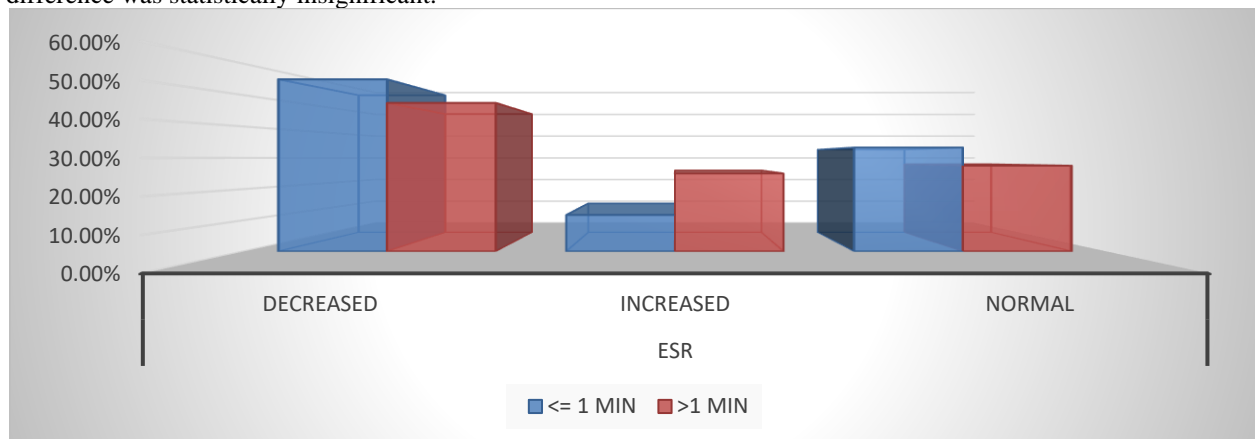
**Fig 3:Duration of seizure VS HSCRPs (N = 100)**

**Table 5:Duration of seizure VS ESR (N = 100)**

		ESR			Total	
		Decreased	Increased	Normal		
Duration of Seizure	<= 1 MIN	Count	33	7	20	60
		%	55.0%	11.7%	33.3%	100.0%
	>1 MIN	Count	19	10	11	40
		%	47.5%	25.0%	27.5%	100.0%
Total		Count	52	17	31	100
		%	52.0%	17.0%	31.0%	100.0%

Chi square test, P value- 0.219

As seen in the above table, most of the study population with seizure persisting for more than 1 minute had decreased ESR (65%) followed by normal ESR (27.5%) . ESR was increased only in 25% of cases and the difference was statistically insignificant.



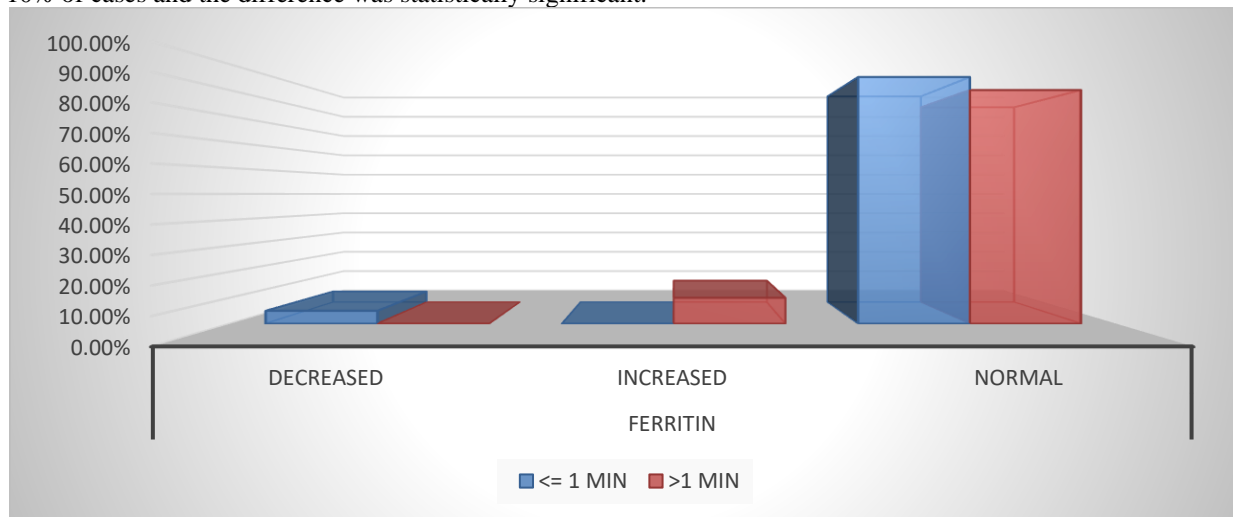
**Fig 4:Duration of seizure VS ESR (N = 100)**

**Table 6: Duration of seizure vs ferritin (N = 100)**

			Ferritin			Total
			Decreased	Increased	Normal	
Duration Of Seizure	<= 1 MIN	Count	3	0	57	60
		%	5.0%	0.0%	95.0%	100.0%
	>1 MIN	Count	0	4	36	40
		%	0.0%	10.0%	90.0%	100.0%
Total		Count	3	4	93	100
		%	3.0%	4.0%	93.0%	100.0%

Chi square test, P value- 0.01

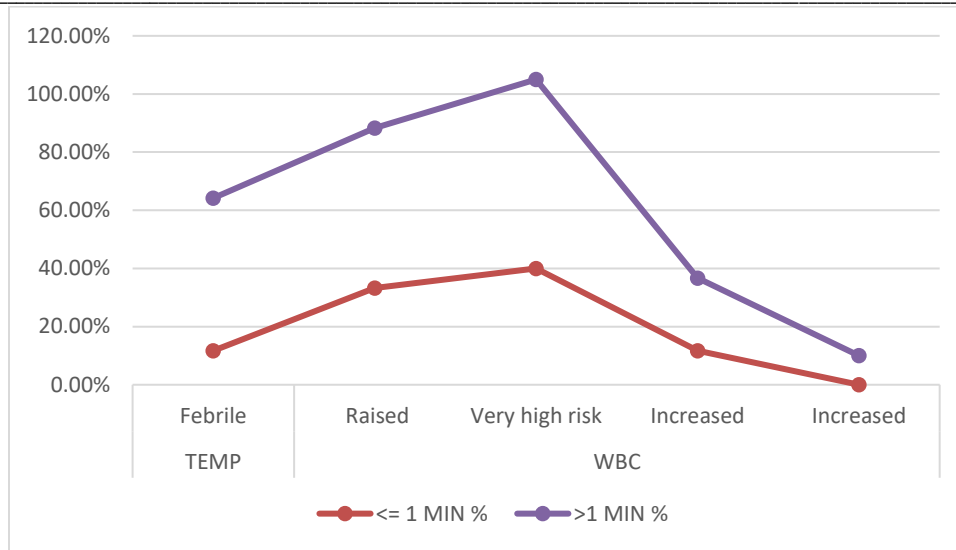
As seen in the above table, among the cases with more than 1 minute of duration of seizure, ferritin was increased in 10% of cases and the difference was statistically significant.



**Fig 5:Duration of seizure vs ferritin (N = 100)**

**Table 7:Comparison of inflammatory markers with duration of seizure**

Duration of seizure		TEMP	WBC	HSCRP				ESR		Ferritin	
		Febrile	Raised	Average	High	Low	Very high	Decreased	Increased	decreased	Increased
<= 1 MIN	Count	7	20	13	11	12	24	33	7	3	0
	%	11.70%	33.30%	21.70%	18.30%	20.00%	40.00%	55.00%	11.70%	5.00%	0.00%
>1 MIN	Count	21	22	2	8	4	26	19	10	0	4
	%	52.50%	55.00%	5.00%	20.00%	10.00%	65.00%	47.50%	25.00%	0.00%	10.00%
Total	Count	28	42	15	19	16	50	52	17	3	4
	%	28.00%	42.00%	15.00%	19.00%	16.00%	50.00%	52.00%	17.00%	3.00%	4.00%



**Fig 6: Comparison of inflammatory markers with duration of seizure**

From the above line diagram it is evident that in patients with seizure duration of more than 1 min, most of them were febrile, with raised WBC counts and values of HSCRP suggestive of high. Although ESR and ferritin were not significantly increased in either groups. As seen in the above table, most of the study population who presented with 1st episode of seizure belonged to the age group up to 25 years (26%)

followed by 26 to 35 years (22%) while most of the study population who were known case of seizure disorder belonged to the age group up to 25 years (36%) and the difference was statistically insignificant. Similarly there was male predominance (76%) amongst study population as compared to female (24%) in both groups and the difference was statistically insignificant [12,13]

**Table 8: Type of seizures vs wbc (n=100)**

		WBC		Total
		Normal	Raised	
Type of seizure	Absence	Count	1	1
		%	1.7%	1.0%
	CPS	Count	3	10
		%	5.2%	10.0%
	GTCS	Count	47	74
		%	81.0%	74.0%
	SPS	Count	3	8
		%	5.2%	8.0%
	Status Epilepticus	Count	4	7
		%	6.9%	7.0%
Total		Count	58	100
		%	100.0%	100.0%

Chi square test, P value- 0.126

As seen in the above table, leukocytosis was observed most commonly in GTCS (64.3%) followed by CPS (16.7%), SPS (11.9%) and Status Epilepticus (7.1%) and the difference was statistically insignificant.

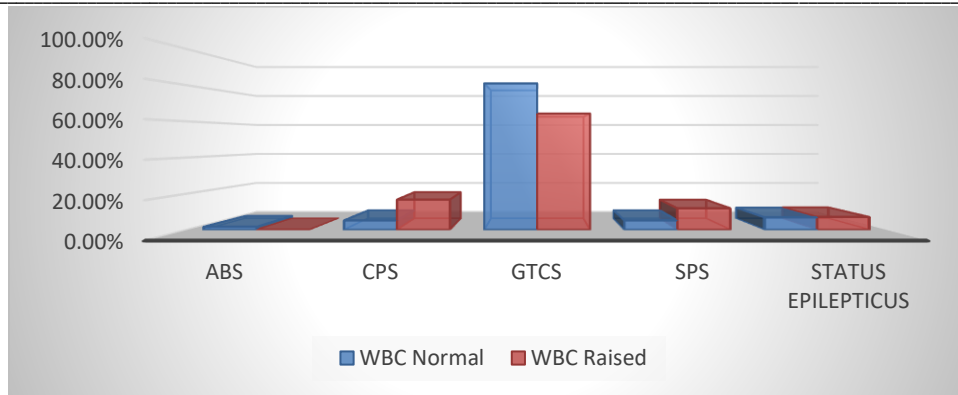


Fig 7:Type Of Seizures Vs WBC (N=100)

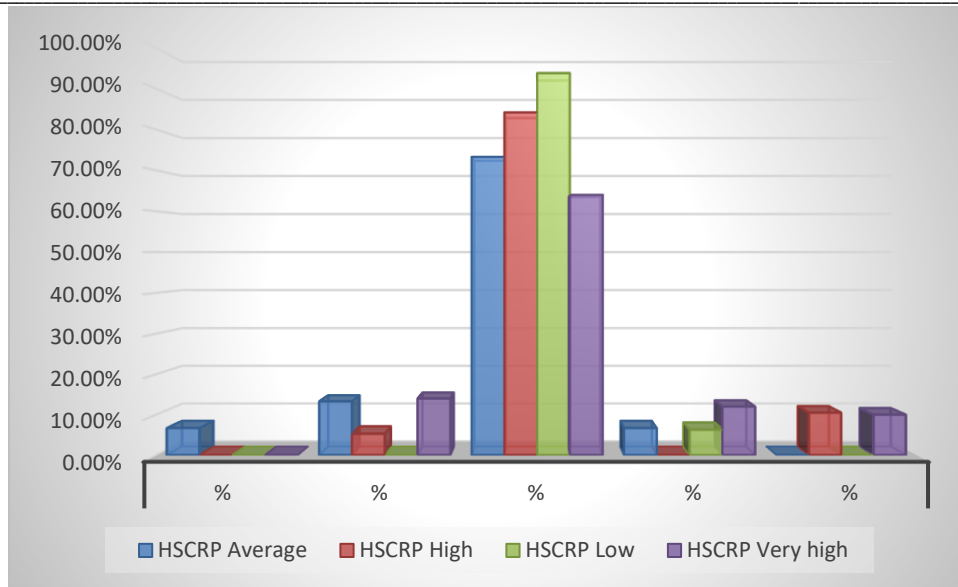
Table 9:Type of seizures VS HSCR P (N=100)

			HSCR P				Total
			Average	High	Low	Very high	
TYPE OF SEIZURE	ABSENCE	Count	1	0	0	0	1
		%	6.7%	0.0%	0.0%	0.0%	1.0%
	CPS	Count	2	1	0	7	10
		%	13.3%	5.3%	0.0%	14.0%	10.0%
	GTCS	Count	11	16	15	32	74
		%	73.3%	84.2%	93.8%	64.0%	74.0%
	SPS	Count	1	0	1	6	8
		%	6.7%	0.0%	6.3%	12.0%	8.0%
	STATUS EPILEPTIC US	Count	0	2	0	5	7
		%	0.0%	10.5%	0.0%	10.0%	7.0%
Total		Count	15	19	16	50	100
		%	100.0%	100.0%	100.0%	100.0%	100.0%

Chi square test, P value- 0.182

As seen in the above table, Very high values of HSCR P was observed most commonly in GTCS (64%) followed by CPS (14%), SPS (12%) and Status Epilepticus (10%) and the difference was statistically insignificant.





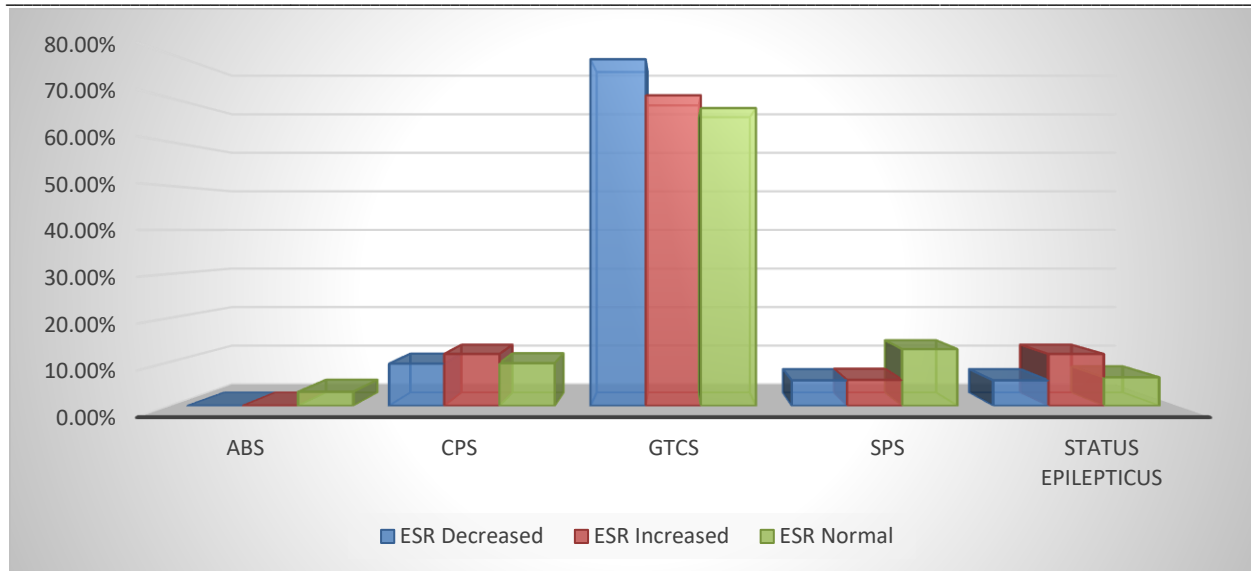
**Fig 8: Type of Seizures VS HSCRP (N=100)**

**Table 10: Type of seizures vs ESR (N=100)**

		ESR			Total	
		Decreased	Increased	Normal		
Type of Seizure	Absence	Count	0	0	1	
		%	0.0%	0.0%	3.2%	
	CPS	Count	5	2	3	
		%	9.6%	11.8%	9.7%	
	GTCS	Count	41	12	21	
		%	78.8%	70.6%	67.7%	
	SPS	Count	3	1	4	
		%	5.8%	5.9%	12.9%	
	Status Epilepticus	Count	3	2	2	
		%	5.8%	11.8%	6.5%	
	Total		Count	52	17	31
			%	100.0%	100.0%	100.0%

Chi square test, P value- 0.792

As seen in the above table, raised ESR was observed most commonly in GTCS (67.7%) followed by SPS (12.9%), CPS (9.7%), and Status Epilepticus (6.5%) and the difference was statistically insignificant.



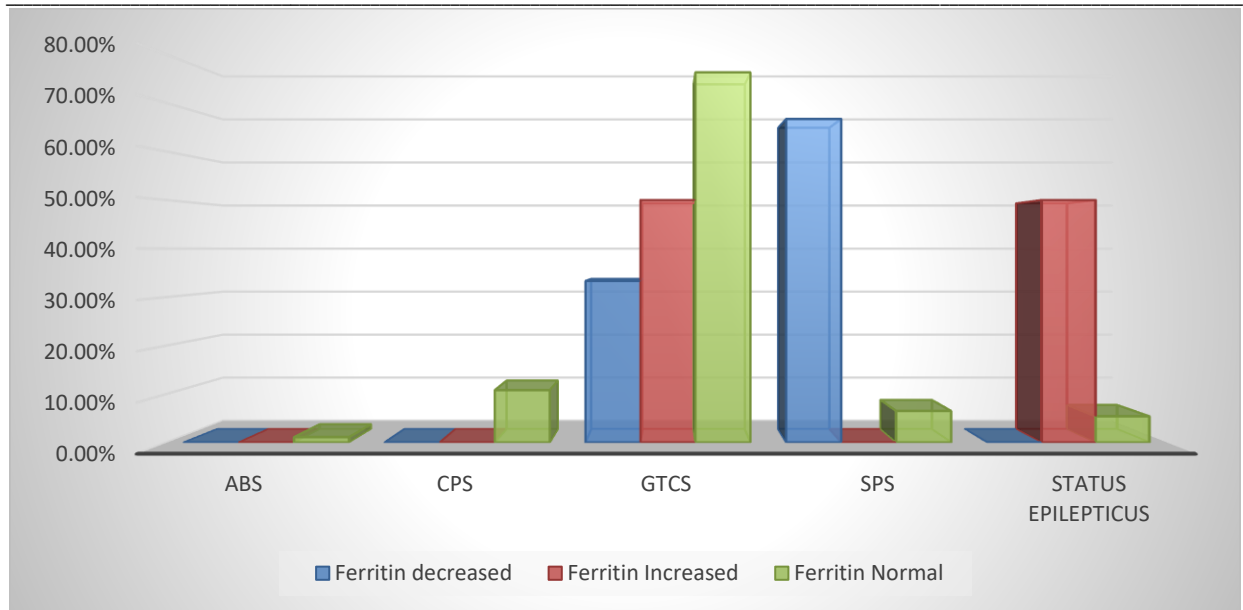
**Fig 9: Type of seizures VS ESR (N=100)**

**Table 11: Type Of Seizures Vs Serum Ferritin (N=100)**

			Ferritin			Total
			Decreased	Increased	Normal	
Type of seizure	ABSENCE	Count	0	0	1	1
		%	0.0%	0.0%	1.1%	1.0%
	CPS	Count	0	0	10	10
		%	0.0%	0.0%	10.8%	10.0%
	GTCS	Count	1	2	71	74
		%	33.3%	50.0%	76.3%	74.0%
	SPS	Count	2	0	6	8
		%	66.7%	0.0%	6.5%	8.0%
	STATUS EPILEPTICUS	Count	0	2	5	7
		%	0.0%	50.0%	5.4%	7.0%
	Total	Count	3	4	93	100
		%	100.0%	100.0%	100.0%	100.0%

Chi square test, P value- 0.792

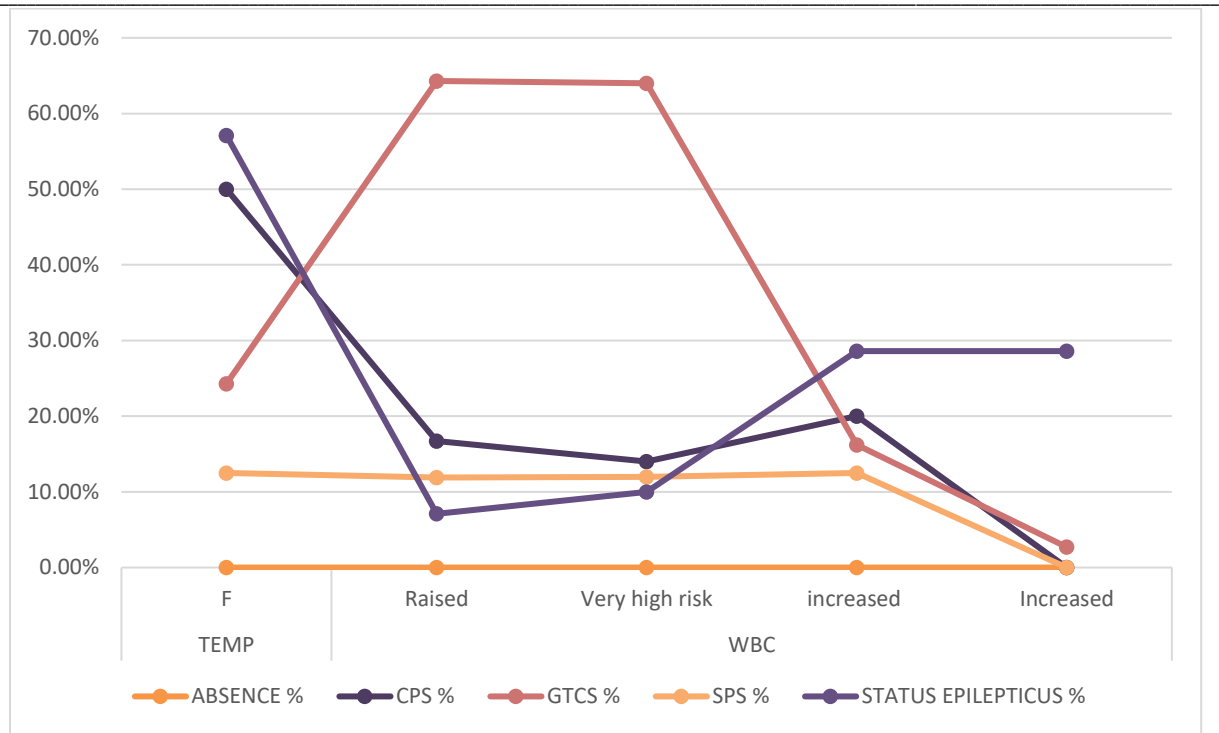
As seen in the above table, raised ferritin was observed most commonly in GTCS (76.3%) followed by CPS (10.8%), SPS (6.5%) and Status Epilepticus (5.4%) and the difference was statistically insignificant.



**Fig 10: Type Of Seizures Vs Serum Ferritin (N=100)**

**Table 12: Trend of inflammatory markers in various type seizures (N=100)**

Type of seizure		HSCRP						ESR		Ferritin	
		F	Raised	Average	High	Low	Very high	Decreased	Increased	Decreased	Increased
Absence	Count	0	0	1	0	0	0	0	0	0	0
	%	0.00%	0.0%	6.7%	0.0%	0.0%	0.0%	0.00%	0.00%	0.00%	0.00%
CPS	Count	5	7	2	1	0	7	5	2	0	0
	%	50.00%	16.7%	13.3%	5.3%	0.0%	14.0%	50.00%	20.00%	0.00%	0.00%
GTCS	Count	18	27	11	16	15	32	41	12	1	2
	%	24.30%	64.3%	73.3%	84.2%	93.8%	64.0%	55.40%	16.20%	1.40%	2.70%
SPS	Count	1	5	1	0	1	6	3	1	2	0
	%	12.50%	11.9%	6.7%	0.0%	6.3%	12.0%	37.50%	12.50%	25.00%	0.00%
Status Epilepticus	Count	4	3	0	2	0	5	3	2	0	2
	%	57.10%	7.1%	0.0%	10.5%	0.0%	10.0%	42.90%	28.60%	0.00%	28.60%
Total	Count	28	42	15	19	16	50	52	17	3	4
	%	28.00%	42.00%	15.00%	19.0%	16.00%	50.0%	52.00%	17.00%	3.00%	4.00%



**Fig 11: Trend of inflammatory markers in various type seizures (N=100)**

It is evident from the following graph that all inflammatory markers except ESR and ferritin, WBC and HSCRP were increased most commonly in GTCS. In most of the types of seizure, i.e. CPS and Status Epilepticus, high basal body temperatures were recorded.

**Discussion**

In the present study, most of the study population who presented with 1st episode of seizure belonged to the age up to 25 years (26%) and 26 to 35 years (22%) while most of the study population who were known case of seizure disorder belonged to the younger age group of less than and equal to 25 years (36%). There was male predominance (76%) amongst study population as compared to female (24%). Similarly in the study by Kaur et al, 2018, among the 100 patients, 65% were males; maximum patients (38%) were in the age group of 21–40 years and 41–60 years, only 9% were aged <20, years and 15% more than 60 years. In relation to seizure-induced differences in CRP levels, the present study reported significant increase in HSCRP levels in GTCS (64%) very similar to Alapirtti et al. who reported the same in SGTCS, and no change in SPS or CPS. In the present study it is observed that WBC levels were increased in 34% of cases with 1<sup>st</sup>

episode of seizure and 50% of known case of seizure H.S. Sohn, et al.[11] reported a little less incidence (37.7%) of the same. Very high levels of HSCRP was seen in 50% of cases with 1st episode of seizure and 50% of known case of seizure. In our study, HSCRP was most commonly reported in generalized tonic clonic seizure (64%) followed by complex partial seizure (14%). Similar results were obtained in the study by Mantovani et al. (2008) where the CRP levels were increased in four out of five patients with secondarily generalized tonic clonic seizure, whereas in partial seizures there was no change after index seizure. As seen in the present study, ESR was increased in 18% of cases with 1st episode of seizure and 16% of known case of seizure[12,13]. It was most commonly increased in Drug Default Seizure (19.4%) followed by CNS Infections (16.1%). In a study by Rahbarimanesh et al., on children with febrile disease, with or without seizures, there was no significant difference regarding ESR levels among the two groups. Raised ESR levels were most commonly associated with generalized tonic clonic seizures[14,15]. As seen in the present study, serum Ferritin was equally increased in both cases with 1st episode of seizure (4%) and known case of seizure (4%). It was increased most commonly in CNS Infections (17.2%) followed by Drug Default Seizure (16.1%), Post stroke seizure (15.1%), Alcohol

withdrawal seizure (15.1%) and Scar Epilepsy (7.52%).

Increased levels of ferritin was most commonly observed in Generalized tonic clonic seizure (76.3%) followed by complex partial seizure (10.8%).

### Conclusion

The study concluded that the overall increase in inflammatory markers was higher in cases with first episode of seizure as compared to known case of seizure. Inflammatory markers except ESR and FERRITIN, WBC and HSCRP were increased most commonly in GTCS. The study also concluded that the markers of inflammation evaluated in the present study cannot not be used as diagnostic markers for different type of seizures since their correlation did not reach the statistically significant value.

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