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Original Research Article

# LEUCOCYTOSIS AND ELEVATED LEVELS OF BLOOD C-REACTIVE PROTEIN IN CHILDREN PRESENTING WITH SEIZURES.

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## ABSTRACT

**Background:** Seizures produce systemic changes including elevation of white blood cell count and C-reactive protein levels (CRP).However, the frequency & severity of the inflammatory response in different types of paediatric seizures is not well researched. Hence, we aimed to study the frequency and degree of systemic inflammatory response (leucocytosis-neutrophilic, high CRP) in seizures.

**Materials and Methods:** This prospective observational study was conducted over a period of 2years. 100 children aged 6 months to 18 years admitted with seizures to emergency department of MVJMC and RH were included. Complete Blood Counts and CRP were sent along with other relevant investigations. Demographic data along with clinical characteristics, leucocyte count and CRP were recorded and analysed.

**Results:** Majority (58%) of our study participants were aged between 1-5 years. 62% of the children were males. Leucocytosis and elevated CRP were seen respectively in 44% and 75% of paediatric seizures. 78.2% of generalised seizures & 37.5% of focal seizures had raised CRP. Leucocytosis was found in 63% of children with seizures for more than 5 minutes and in status epilepticus. There was no significant difference in occurrence of leucocytosis and raised CRP in paediatric seizures with and without bacterial/central nervous system infection.

**Conclusion:** Paediatric seizures are commonly associated with inflammatory response in form of elevated CRP and leucocytosis. Generalised seizures are more commonly associated with elevated CRP. Prolonged seizures and status epilepticus are associated with leucocytosis.

**Keywords:** Leucocytosis, raised CRP, pediatric seizures, inflammatory response, status epilepticus.

## INTRODUCTION

A seizure is a transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. Approximately 4-10% of children experience at least one seizure, in the first 16 years of life.[1]Common causes of seizures in paediatric age group are symptomatic seizures secondary to metabolic, infectious, vascular, structural malformations, trauma or other aetiologies, epilepsy and febrile seizures. It is important to find out type and cause of seizure as the management and prognosis depend on them.

Various studies have showed that seizures, mainly epilepsy produce systemic inflammatory response like increased body temperature, raised white blood cell (WBC) counts, raised biomarkers of inflammation like CRP.[2]This is due to the activation of the immune system and the release of pro-inflammatory cytokines. Some of the possible pathological mechanisms can be blood-brain barrier disruption, neuro inflammation, oxidative stress,

excitotoxicity, genetic predisposition, infection and autoimmune disorders.[3]

Inflammatory responses like neutrophilic leukocytosis, raised CRP are commonly taken as supportive evidence for bacterial infection and has led to inadvertent use of antibiotics. There are very few studies on degree of inflammatory response in various pediatric seizures.[4]Hence, we intended to study the presence of inflammatory response and its extent in paediatric seizures with respect to their aetiology, duration, type and its role in the prediction of bacterial/CNS infection in a child presenting with seizures.

## MATERIALS AND METHODS

A prospective observational study was done in MVJMC& RH, a tertiary care teaching hospital of rural Bangalore over a period of 2 years (September 2022 to September 2024). 100 cases aged between 6 months to 18 years presenting with seizures to emergency department, were enrolled in study. Children with pre-existing inflammatory disorders, who had seizures secondary to severe respiratory distress and those with last seizure episode 24 hours prior to admission were excluded. Institutional Ethical Committee approval and written informed consent were obtained prior to beginning of the study.

Subjects were stabilized and managed as per existing seizure protocol.Detailed history including demographic details, seizure type and duration of seizures and relevant data was collected as per the proforma. Cases underwent routine investigations, CBC with differential counts and CRP at admission. Cerebrospinal fluid (CSF) analysis (cell count, protein sugar & culture) was done in children and infants with suspected CNSinfection like the presence of unexplained prolonged altered sensorium orfever with convulsions. Neuroimaging and other required investigations were done if needed.Causes of seizures were evaluated and subjects were categorized as seizures with or without CNS/bacterial infection.To determine whether differentiation regarding presence of bacterial /CNS infection is possible based on presence and degree of raised inflammatory markers, comparison of inflammatory markers was done among paediatric seizures with and without bacterial /CNS infection.

Data was analysed using SPSS 22 software and frequency of raised inflammatory markers in paediatric seizures and their association with type duration of seizures and bacterial /CNS infection was studied.

## RESULTS

Among the study cohort majority (58%) of children were aged between 1-5 years, followed by 16% between 6-10 years, 14% aged 6 months–1year and 12% between 11-18years.Male gender was predominant (62%), with male to female ratio of 1.6:1.Developmental delaying the form of isolated or global developmental delay was observed in 18 cases. 92% of children presented with generalized tonic clonic/tonic/clonic seizures (GTCS)and 8% had focal seizures. Majority of children (89%) had seizureduration of less than 5 minutes.Among 11children who presented with status epilepticus, 7 children had seizures lasting for 5–10 minutes, 3 children had for 10–30 minutes and one case had seizures for more than 30 minutes.

The most common cause of seizures in our study was febrile seizures (49%) secondary to various infections, followed by seizure disorder in 44% of cases. Other etiologies (7%)were neurocysticercosis, encephalitis, stroke, hypertensive encephalopathy, structural malformation and IEM. We observed inflammatory markers like elevated CRP in 75% and leucocytosis in 44% of children. CRP levels above 10mg/dl was observed in 47% of the cases. 43% of children presenting with seizures had leucocyte count between 11000 to 20000cells/mm3. Leucocyte count> 20,000 cells/mm3 was seen in one child.(Shown in Table 1)

The association of degree of leucocytosis with different types of seizures was not statistically significant (generalized seizures 43.4% Vs focal seizures 50% with p=0.72).78.2% of children with generalised seizures had raised CRP as compared to 37.5% in focal seizures which was statistically significant(p=0.011)as shown in Table 2 (The correlation of elevated inflammatory markers with type and duration of seizures).48.9% of subjects with generalised seizures compared to 25% of subjects with focal seizures had CRP more than 10mg/dl which was statistically significant. (p=0.0038).

Leucocytosis was found to be more common in seizures lasting >5 minutes compared to children with seizures <5 mins which was statistically insignificant (63.6% Vs 41.5%, p=0.16).Among the children who had seizures for >5min, leucocytosis of 11000 to 20000 cells/mm3was seen in54.5% of cases & leucocyte count of >20000 cells/mm3 in 9.2% of cases.Raised CRP was found to be more common in seizures < 5 minutes (78.6%) compared to children with seizures lastedfor >5 minutes (45.5%). This was statistically significant (p=0.016).CRP more than 10mg/dl was found in 27.3% of subjects with status epilepticus compared to 49.2% of subjects presenting without status epilepticus which was statistically insignificant (p= 0.06).

There was no statistically significant difference in leucocytosis or raised CRP in seizures with and without fever.There were 6 children with CNS/bacterial infections. Leucocytosis was more frequently observed in paediatric seizures with bacterial or CNS infection (66.6%) compared to those without such infection (42.5%). However, it was statistically not significant (p=0.24). Leucocyte

count more than 20000 cells/mm3 was seen only in onechild with seizures with CNS/bacterial infection (16.7%). Raised CRP was more commonly observed in paediatric seizures without CNS/bacterial infection and this difference was statistically insignificant (p=0.14). CRP more than 10mg/dl was seen almost equal in paediatric seizures with(50%) and without(46.8%) CNS/bacterial infections

**Table 1: Baseline characteristics ofpatients with seizures**

| Characteristics | Percentage |
|---|---|
| **Number of participants** | 100 |
| **Gender: Male** | 62% |
| **Age of participants** | |
| <1yr | 14% |
| 1 yr – 5 yr | 58% |
| 6 yr – 10 yr | 16% |
| 11 yr – 18 yr | 12% |
| **Developmental delay** | **18%** |
| Isolated motor delay | 7% |
| Isolated speech delay | 5% |
| Global developmental delay | 6% |
| **Type of seizures** | |
| GTCS | 92% |
| Focal seizures | 8% |
| **Duration of seizures** | |
| <5min | 89% |
| 5 – 10 min | 7% |
| 10-30 min | 3% |
| >30 min | 1% |
| **Aetiology of seizures** | |
| Febrile seizures | 49% |
| Seizure disorder | 44% |
| others | 7% |
| **Elevated inflammatory markers** | |
| CRP | 75% |
| Leucocytosis | 44% |
| **Degree of elevated CRP (mg/dl)** | |
| <6 | 25% |
| 6 TO 10 | 28% |
| >10 | 47% |
| **Degree of leucocytosis (cells/mm$^3$)** | |
| <11,000 | 56% |
| 11,000 – 20,000 | 43% |
| <20,000 | 1% |

GTCS- Generalized Tonic Clonic Seizures

**Table 2: Correlation of elevated inflammatory markers with type and duration of seizures**

| | **Leucocytosis N(%)** | **Elevated CRP N(%)** |
|---|---|---|
| Type of seizures:<br>• Focal<br>• Generalised | 4(50%)<br>40(43.4%)<br>p-value – 0.72 | 3(37.5%)<br>72(78.2%)<br>p-value – 0.011* |
| Duration of seizures:<br>• <5 minutes<br>• >5 minutes | • 37(41.5%)<br>• 7(63.6%)<br>p-value- 0.16 | • 70(78.6%)<br>• 5(45.5%)<br>p-value- 0.016* |
| Status epilepticus:<br>• Present<br>• Absent | • 7(63.6%)<br>• 37(41.5%)<br>p-value- 0.164 | • 5(45.5%)<br>• 70(78.6%)<br>p-value- 0.01* |
| Seizures with fever:<br>• Present<br>• Absent | • 29(42%)<br>• 15(48.4%)<br>p-value- 0.55 | • 52(75.4%)<br>• 23(74.2%)<br>p-value- 0.91 |
| CNS/bacterial infection:<br>• Present<br>• Absent | • 4 (66.6%)<br>• 40 (42.5%) | • 3 (50%)<br>• 72 (76.5%) |

| | | |
|---|---|---|
| | p-value- 0.24 | p-value- 0.14 |

## DISCUSSION

We studied inflammatory response in 100 children presenting with seizures. In our study majority of the children presenting with seizures belonged to the age group of 1 to 5 years which was also observed in a similar study by Chen CY et al. where the subjects largely were of 1-6 years of age.[5]Higher incidence of seizures among 1 to 5 years of age group could be attributed to higher incidence of febrile seizures of around 2% to 5%and genetic etiology of majority of childhood seizures.Theongoing maturation of neurons during infancy make the children susceptible to higher incidence of febrile seizures.Males had higher representation of seizures than females, which is comparable to that found in the study done by P Satish Chandra et al.[6] The increased prevalence of febrile seizures among male children could explain this male predominance.

Overall,generalized seizures were the most common phenotypic presentation when compared to focal seizures in our study. In the same way generalised seizures were more common in children less than 5 years of age compared to > 5 years where focal seizures were predominant. Similar studies by P Satish Chandra et al. and Kaikho et al. showed that generalised seizures were the most common type in children less than 5years of age and again this could be due to the more prevalence of febrile seizures in this age group where simple febrile seizures with generalised tonic clonic phenotype have higher presentation.[6,7]

In our study, majority of children presenting with seizures had normal development with 12%having delayed milestones in the form of isolated motor/speech delay and 6%had global developmental delay which was in agreement to studies by P Satish Chandra et al. where out of 127 children 90.7% had a normal development and in the Bharathi M et al. study, normal history of development was seen in 95% of cases and 5% of children had abnormal development.[6,8]

In present study, there was no statistically significant difference in occurrence of leucocytosis in generalised and focal seizures. However, raised CRP was significantly more observed in generalised seizures(78.2%) compared to that in focal seizures (37.5%) (p value of 0.011). Association of raised CRP with generalized seizures was also reported in a study done by Ishikawa et al.where it was found that Hs-CRP levels are significantly higher in daily motor seizures than intermittent seizures.[9]This can be explained by the fact that generalised seizures cause more neuroinflammation due to excitotoxicity which can lead to an inflammation like response in seizures.[10]However contrary to expected outcome, occurrence of raised CRP and its degree was significantly less in children with status epilepticus in our study.

In our study, Leucocytosis was more commonly seen in children with seizures lasting more than 5 minutes and in status epilepticus. This is in agreement with other studies done by Bakhtiari et al. which showed a significant relationship between the leucocytosis and convulsion in patients with longer than 15 minutes convulsion (P = 0.03) and Aydogan et al. study concluded that afebrile children with status epilepticus i.e.prolonged seizures may lead to peripheral leucocytosis.[11,12] This possibly suggests that increased duration of seizures increases the stress like response and also tissue inflammation which can be the probable cause of raise in leucocyte count and CRP.[13]

We also observed that in our study,the seizure cases with or without associated fever prior to onset of seizuresdid not have statistically significantleucocytosis and CRP between the groups.No significant difference in occurrence of leucocytosis in seizures with and without fever was also reported in the study done by Mohebbiet al.[14] Leucocytosis is likely to be a stress response during seizures and need not always be associated with infection. In agreement to this, in our study, even though leucocytosis was more commonly seen in seizures associated with CNS/bacterial infection (66.6%) compared to seizures without associated CNS/bacterial infections (42.5%), the difference was not statistically significant. However, leucocyte count of more than 20000cells/mm3 was significantly associated with presence of CNS/bacterial infection. With respect to CRP however, there was no significant difference in occurrence and degree of increase in seizures with or without CNS/bacterial infections. A study done by Sohn et al. on inflammatory markers in seizures observed no significant difference in leucocytosis with regard to the presence or absence of infection and contradictorily there was mild elevation in CRP levels in patients without infection compared to those with infection.[2]

Thus, presence of leucocytosis or raised CRP do not help in differentiating seizures with and without bacterial / CNS infections. However, leucocyte count more than 20000cells/$mm^3$ should arouse the suspicion of associated bacterial/CNS infection.

## CONCLUSION

Paediatric seizures are associated with inflammatory response in form of elevated CRP and leucocytosis. Raised CRP and CRP values more than 10mg/dl are more commonly observed in generalised seizures than in focal seizures, whereas, leucocytosis and higher degree of leucocytosis is more common in prolonged seizures and status epilepticus. Leucocytosis and raised CRP are not reliable

markers for differentiating presence of CNS/bacterial infections in children presenting with seizures. However, Leucocyte count more than 20000cells/$mm^3$should arouse suspicion of CNS/bacterial infection.

**Limitations**

Factors like dehydration, vomiting, trauma which can also cause leucocytosis were not considered. Relatively small sample size was studied.

**Conflicts of interest:** None

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