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Original Research Article

Evaluating the role of hemogram based parameters in febrile seizures

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ABSTRACT

Background: One of the most common childhood neurological disorders is febrile seizures (FS). Parents may have trouble describing the events pertaining to seizures, which might lead to aberrations in the diagnosis and classification of FS. Hence, objective biomarkers to predict and classify FS will be clinically beneficial. The aim of this study was to evaluate role of hemogram based parameters (NLR, PLR, RDW, MPV) in the outcome of children with febrile seizures (FSs) and in differentiating between simple and complex febrile seizures.
Methods: A total of 50 patients with FSs (group A) who were hospitalized in our hospital were selected. Fifty patients with fever and without seizures (group B). The results of hemogram were collected retrospectively and analysed.
Results: The hemogram analysis showed that hemoglobin (Hb) in group A was significantly lower than in the group B ($p<0.05$). The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), MPV and RDW in group A was significantly higher than in group B. The MPV and NLR values in the CFS group was higher in comparison to SFS group ($p<0.05$).
Conclusions: As statistically significant differences were found in the hemogram parameters like HB, RDW, MPV, NLR PLR between febrile seizure group and non-febrile seizure group, these parameters can aid in diagnosing the same. High NLR and MPV levels may be able to serve as simple yet effective laboratory indicator for distinguishing between simple and complex febrile seizures.

Keywords: Febrile seizures, Hemogram, Objective biomarkers

INTRODUCTION

Febrile seizure (FS) is the most common type of seizure occurring during the childhood period. It typically occurs between six months and five years of age, with a temperature above 38°C.[1] Unlike simple febrile seizures, complex FS can affect the development of children. Therefore, objective biomarkers to diagnose FS as well as differentiate the complexity is the need of the hour.

The suggested pathogenesis of febrile seizures is multifactorial but mainly based on the cytokine release and genetic susceptibility to raised inflammatory responses that accompany fever and provoke seizures.

Hemogram analysis is the most basic laboratory investigation available, that is cost-effective, rapid, and easy to perform. Apart from providing an insight into the basic blood parameters, the associated indices have a potential to serve as biomarkers for various diseases.

Many authors point out that iron deficiency anaemia in children is an important risk factor for occurrence of febrile seizures. The presence of iron in haemoglobin plays an important role for oxygen transport, fever can worsen the effect of anaemia further decreasing the oxygen level that could cause convulsions. RDW is the degree of anisopoikilocytosis, normal range being 11.5-14.5%.[2] It has been used to differentiate types of anaemias, and an increase in this value is seen in IDA.

Recent studies have also shown that an increase in RDW can be associated with underlying metabolic abnormality, inflammation and oxidative stress thus making it a useful predictor for febrile seizure.[3]

Neutrophils and lymphocytes take part in cell-mediated inflammatory responses, and a higher NLR is linked to higher levels of inflammatory substances like tumor necrosis factor alpha, IL-6, IL7, IL-8, IL-12, and IL-17 that play a role in the pathogenesis of febrile seizures. The number of neutrophils can temporarily and rapidly increase during intense skeletal muscle activity.[4,5] Neutrophil lymphocyte ratio is a cost effective, easy to calculate measure that has been used by many clinicians. It is calculated by dividing the absolute neutrophil count by absolute lymphocyte count. Normal range taken in children is 1-3. It has been associated with many inflammatory and infectious conditions like autoimmine disorders, asthma, cardiovascular diseases, sepsis, pneumonia, malignancies etc.[8,10]

Recent studies shown that in addition to haemostasis, platelets play an important role in inflammation and immunity thus showing a relationship with febrile seizures.[9] Mean platelet volume (MPV) is the degree of variation in the size of platelets and the rate of its production and is used as an indicator of platelet activation and severity of inflammation.

MPV is also a marker of inflammation. MPV values have previously been studied extensively in cerebrovascular diseases and shown that neuronal cell damage would cause an increase in MPV. Normal range being 7-12 fl.

PLR is a ratio between the absolute platelet count and absolute lymphocyte count, the cut off value being 60. Various studies have evaluated the same and have different cut off values taken as per their lab reference ranges. PLR reflects changes in platelet (PLT) and lymphocyte counts. It can evaluate the severity of infectious diseases, as well as reflect or assess the degree of thrombosis and inflammatory response in the body and has previously been used in many acute and chronic inflammatory conditions.[11] There are very few studies on the utility of the same in febrile seizure.

Hence, we performed a retrospective analysis to identify the role of these hemogram related parameters and their variations in FS, as well as in differentiating between simple and complex FS.

METHODS

This research represents a retrospective study collected from the case records of all the children admitted with febrile seizures (group A) and those with fever not associated with seizures (group B) for a period of 6 months from January to June 2023. The study was conducted in the department of pediatrics in AJ Institute of Medical Sciences.

Inclusion and exclusion criteria

Of the 50 patients selected with febrile seizures, most were children with acute upper respiratory tract infection. Children with HIE, epilepsy, brain injury, inborn errors of metabolism and mental retardation were excluded.

A diagnosis of FS was made according to the 2011 American Academy of Pediatrics (AAP) criteria. 12 A febrile seizure is a seizure accompanied by fever (temperature ≥ 100.4°F or 38°C by any method), without central nervous system infection, that occurs in infants and children 6 through 60 months of age. They were further divided into simple and complex febrile seizures (SF and CFS). Simple febrile seizures were defined as primary generalized seizures that lasted for less than 15 minutes and did not recur within 24 hours. Complex febrile seizures were defined as focal, prolonged (≥15 minutes), and/or recurrent within 24 hours.

In group B (controls) 50 patients of similar age and who had been hospitalized during the same period for acute upper respiratory tract infection, with fever but no seizures, and where the fever ran its course within three days were selected and hemogram analysis was performed.

Analysis of hemogram

2 ml of venous blood was drawn within half an hour following admission and put into a tube containing EDTA. The samples were sent for whole blood cell analysis. Complete blood count analysis was performed using an automatic blood cell analyzer. The hemoglobin, platelet count, absolute neutrophil count and absolute lymphocyte count, mean platelet volume and RDW were noted. A cut off value of 12 fl was taken for MPV and 14.5% for RDW.

NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Cut off value was taken as 3. PLR was calculated by platelet count divided by absolute lymphocyte count, cut off taken was 60.

These parameters were observed in both group A and group B and the results were tabulated and analysed. Also these parameters were compared between those with SFS and CFS under group A.

Statistical analysis

Analyses were conducted using the SPSS Statistics software (v20) program. A Chi-square test (χ^2) or Fisher's exact test was used for the data enumeration. Normally distributed variables were expressed as the mean±standard deviation (SD) and were compared with independent sample t-tests. All p values less than 0.05 were considered statistically significant.

RESULTS

The study included 50 children (mean age 2.9±1.6 years old) in the group A, including 15 patients with CFS (mean age 4.0±2.4 years old) and 35 patients with SFS (mean age 2.7±1.2 years old). The control group included 50 children (mean age 3.4±1.8 years old) (Table 1).

Table 1: Age distribution.

Age	Mean	SD
Case	2.9	1.6
Controls	3.4	1.8

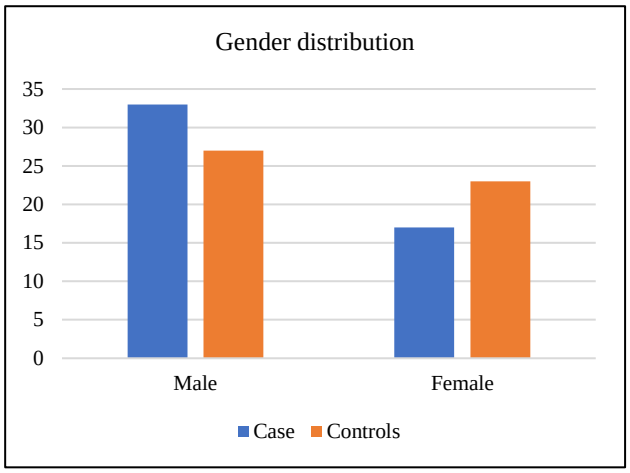

Figure 1: Gender distribution.

Group A had a higher proportion of males than group B (33 versus 27) (Figure 1). The mean temperature in group A and B was comparable (101.22±1.23°F versus 100.86±1.17°F).

There was no significant difference in age, sex or body temperature.

Table 2: Mean values between the two groups.

Parameter	Group A	Group B	P value
HB	10.12±1.09	12.11±1.2	<0.001
MPV	12.62±1.39	9.03±1.31	0.044*
RDW	15.5%	13.8%	0.002*
NLR	4.32±2.41	3.52±2.86	0.041*
PLR	118.45±64.88	102.33±76.87	<0.05*

When we compared the mean values of hemogram parameters (Table 2), we observed that hemoglobin levels were lower in group A as compared to group B and was statistically significant. Mean platelet volume (MPV) and RDW levels in group A was significantly higher than in the group B ($p<0.05$). Neutrophil-to-lymphocyte ratio was increased in both the groups but among the two groups the values in group A was higher than in group B and this difference was statistically significant (p 0.041). Similarly, platelet-to-lymphocyte ratio (PLR) was higher in both the groups but values in group A was higher than in the group B (118.45±64.88 versus 102.33±76.87; $p<0.05$), with a statistically significant difference between the two groups.

Table 3: differences between parameters for differentiating of simple and complex partial seizures.

Parameters	Simple FS	Complex FS	P value
Hemoglobin	12.35±1.25	11.64±1.36	0.063
RDW	13.7%	12.8%	0.377
Mean platelet volume	9.46±1.56	12.40±1.53	0.045*
Neutrophil lymphocyte ratio	3.52±2.86	4.32±2.41	<0.001*
Platelet/lymphocyte ratio (PLR)	106.22±77.96	80.15±32.91	0.125

When we correlated the hemoglobin values (Table 3), CFS group had lower Hb values than in SFS group, but this value was not statistically significant. RDW was not raised more than the cut off values in both the groups neither was there any statistically significant difference noted among the two groups. MPV was higher in CFS group in comparison to SFS group with statistically significant difference (p-0.0045). NLR values were higher in both groups but between the two groups, it was higher in CFS group and this difference was statistically significant ($p<0.05$). PLR was higher than the cut off value in both the groups, but the difference among the two groups was not statistically significant.

This shows that these parameters can be used to differentiate between CFS and SFS.

DISCUSSION

The majority of studies about FS in the literature focus on the risks associated with FS, the development of epilepsy, FS recurrence, treatment and prophylaxis. Besides clinical identification, some recent studies have evaluated the role of laboratory parameters in the differentiation of FS types. It has been suggested that there is currently no laboratory test with a specifically proven value in the management of a child having FS, and these tests only become helpful when accompanied by symptoms and findings of an important disease. While no investigation has been recommended for SFS, it is recommended that clinicians should carry out further investigations in patients with CFS due to the potential long-term risks.[7]

At this time, there is a growing body of information that points to the possibility of a connection between FSs and inflammation.[13] Inflammation is the immune defence response that takes place when an organism is infected by external pathogenic microorganisms or when it is stimulated by injury. Inflammation can also be triggered by a foreign substance entering the body. During this process, many different subtypes of immune system cells are involved. Some of these cells include monocytes, eosinophils, lymphocytes, and macrophages. Patients diagnosed with FSs exhibit considerable activation of their immune systems. During an infection, immune cells like macrophages and lymphocytes are prompted to produce pro-inflammatory cytokines like IL-1, TNF-α, and IL-6 in response to the pathogen. Additionally, the primary immune system cell subtypes like neutrophils, lymphocytes, monocytes, macrophages, basophils, eosinophils, dendritic cells, and mast cells participate in inflammation as a mechanism of innate immunity. In patients with FS, immune system activation is clearly important.[14]

In our study haemoglobin level was lower in the febrile seizure group in comparison to the control group. Some neurotransmitters, including monoamine and aldehyde oxidase, have slower metabolic rates when there is an iron deficit (ID). The idea that iron may be involved in the commencement of a convulsion was supported by several studies. Also, these results may be due to dehydration of children with FS.[5,6] Fluid deficit may cause cellular dehydration and electrolyte shift which decreased seizure threshold which. The result of this study was similar to a study conducted by Liu et al.[5]

Also, the hemoglobin levels were lower in the CFS group in our study in comparison to SFS, though not statistically significant. Anemia could accelerate the development of FS or perhaps cause it, according to earlier studies. Although there were fewer anaemic patients in the CFS group than in the SFS group in the current study, the mean Hb value was still lower in the CFS group. This was like the study conducted by Ornek. Due to the retrospective nature of the current investigation, and the unequal number of patients in the simple and complex febrile seizure group, we are unable to make any assumptions about the connection between anaemia and type of febrile seizure.

In our study, we found that there is a statistically significant difference between NLR and PLR between Febrile seizure group and controls. In a study by Romanowska et al, neutrophil count was significantly lower in the group of children with fever without seizures than in the group of children with FS (48.48 versus 62.55; $p<0.001$).[14] The number of neutrophils can temporarily and rapidly increase during intense skeletal muscle activity (e.g., seizures, chills), may be the result of an inflammatory reaction (after 4-5 hours) or may be associated with the presence of circulating toxins in blood. Neutrophils are the specialised cells of the innate immune system that aid in host defence by phagocytosing and producing reactive oxygen species. They can induce the secretion of several inflammatory cytokines associated with the risk of FS, especially IL-1β and TNFα play an important role in the pathogenesis of FS hence can be hypothesized as the reason for increase in this ratio in the febrile seizure group.

An earlier study by Goksugar et al on 58 children with SFS and 38 with CFS revealed a substantial difference, with a much higher NLR ratio in CFS. Similar findings were made in the study of Yigit et al, which found that the CFS group's NLR ratio was high hypothesizing that this increase could be due to the longer and sustained contraction of muscles during CFS in comparison to SFS leading to increase skeletal muscle activity and further increase in NLR.[6,7] Higher levels have also been observed in this study in CFS group, which was statistically significant and similar to these studies.

The mean platelet volume (MPV) and the platelet count are two important indicators for determining the severity of an infection.[15,16] Elevated MPV is an indicator of larger, more reactive platelets resulting from an increased platelet turnover, and it may be used as an indicator of platelet activation and severity of inflammation.

In a study by Tang et al, they observed that platelet count and MPV served as a marker to differentiate between those with febrile seizures and those with seizures unrelated to fever, as well as isolate those with complex febrile seizures.[17] Serotonin, dopamine, epinephrine, histamine, and GABA are few of the pro-inflammatory and regulatory mediators that platelets can store in their granules for later release at the sites of inflammation or tissue injury during platelet activation. Furthermore, when neutrophils have attached to activated endothelium, the activated platelets may bind to neutrophils. Neutrophil express cytokines and adhesion molecules, both can be stimulated by platelet-neutrophil interactions. In addition, Ozaydin discovered that the MPV of a CFS group was greater than that of a SFS group when the two types of groups were compared.[18]

This was similar to the findings of the present study where the MPV was higher in the FS group in comparison to control group, also it was higher in CFS group than in the SFS group. The PLR is also an effective and simple thrombo-inflammatory marker. It has been suggested to be used as a predictive and prognostic parameter in several conditions, including cardiovascular diseases, pneumonia, hepatitis B and C, vestibular neuritis, thyroid disorders and malignancies. Platelet lymphocyte ratio was significantly higher in the febrile seizure group and was statistically significant which was consistent with the study conducted by Ornek et al.[19] There was no statistically significant difference between SFS and CFS groups, which was not in line with study conducted by Ornek et al probably due to the lesser

number of children with CFS in this study in comparison to SFS group.

Limitations to this study are the retrospective study design and small sample size which might have some conflicting conclusions in comparison to previous studies.

CONCLUSION

This is one of the few studies examining the connection between pediatric FS types and hemogram parameters. Despite the relatively small sample size of this study, we think that the results may aid in diagnosing FS and distinguishing between different FS types, particularly in patients with an unclear seizure history, utilizing the Hb, RDW, MPV, NLR, and PLR. Additionally, a combined evaluation of PLR and NLR values would appear to be more suited for the assessment of inflammation than just using platelet, WBC, or lymphocyte counts alone. We emphasize the need for bigger prospective research on this topic because this was a retrospective observational study on a small patient population. Also, follow-up data might be more relevant to predict the efficacy of these biomarkers in febrile seizure outcomes.

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