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Research Article

Lymphocyte

A cross sectional study of neutrophil to lymphocyte ratio in patients with benign paroxysmal positional vertigo

Azeez Vallur A.[1*]

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[1*] Abdul Azeez Vallur, Associate Professor, Dr. V.R.K. Womens Medical College, Hyderabad, Telangana, India.

Background: Benign paroxysmal position vertigo (BPPV) is a disorder which arises due to problem in inner ear. It is the most common cause of vertigo. **Aim:** This study evaluates the hs CRP, ESR, NLR, PLR, MHR and bilirubin levels in BPPV patients and compare with levels in healthy subjects. **Materials and Methods:** This study is a prospective study which was conducted with 120 newly diagnosed BPPV patients and in 90 patients, age and sex matched. **Results:** The patients were aged between 15 and 75 years. Females were higher than males in both the groups. Smoking rate was higher in-patient group when compared to the control group. Significant lower levels were observed in BPPV patients for vitamin B12, haematocrit, creatinine, urea, fT4, lymphocyte, total, direct, indirect bilirubin levels. HDL, SGOT, ESR values were significantly higher in BPPV patients. Mean neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), MPV values were higher significantly in BPPV patients when compared to healthy control patients. Neutrophil, platelet, monocyte, MHR, CRP were almost similar in both the groups. **Conclusion:** The potential biomarkers of BPPV were neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), MPV, erythrocyte sedimentation rate (ESR) and bilirubin levels. The NLR levels were significantly higher in BPPV patients.

Keywords: Neutrophil-Lymphocyte ratio, Benign paroxysmal positioning vertigo

Corresponding Author

Abdul Azeez Vallur, Associate Professor, Dr. V.R.K. Womens Medical College, Hyderabad, Telangana, India.

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Introduction

A common cause of recurrent vertigo which was characterized by perception of movement of the surrounding objects with brief attacks is Benign paroxysmal position vertigo (BPPV) [1]. BPPV was the common cause of recurrent vertigo. After sudden head movements and canalolithiasis of the posterior semicircular canal, vertigo attacks occurs. The quality of life with reduced daily living activities is impacted by BPPV and morbidity and medical costs are increased and also impairs psychosocial functioning [2]. In elderly patients, the BPPV incidence is significantly higher, but it occurs in any age. BPPV was experienced by approximately 9-11% of patients over 70 years. It is of high importance that the risk factors of BPPV is to be known because of its high incidence. In general practise, some atypical cases are misdiagnosed. Risk of falls and high morbidity are associated with unrecognised diagnosis [3]. The etiological factors in BPPV are inflammation and traumas in the neck or head. Additionally, stress related inflammation might be caused by vertigo associated anxiety. From the blood samples, inflammatory biomarkers show association with the diagnosis of BPPV [4]. High sensitive C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR) are the most widely used inflammatory markers in current clinical practice [5]. In patients with neurological diseases, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are novel inflammatory biomarkers which are calculated from white blood cell count. Inflammation is associated with increased monocyte count and decreased levels of HDL cholesterol (HDL-C). A new inflammatory biomarker is monocyte to HDL-C ratio (MHR). In various diseases, high bilirubin levels were related with anti-inflammation and anti-oxidation. In patients with coronary artery disease, kidney failure, pulmonary embolism, chronic obstructive pulmonary disease and migraine, lower bilirubin concentrations were detected. Worse prognosis of inflammatory bowel disease is associated with higher mean platelet volume (MPV). This study evaluates the hsCRP, ESR, NLR, PLR, MHR and bilirubin levels in BPPV patients and compare with levels in healthy subjects.

Materials and Methods

This study which was conducted for a period of one year from January 2017 to January 2018,

Study done as hospital-based cross-sectional study and was conducted in the Department of Otorhinolaryngology with 120 newly diagnosed BPPV patients and in 90 patients.

Inclusion criteria: Diagnosed with BPPV satisfying the following criteria were included: A) Recurrent attacks of positional vertigo provoked by lying down or turning over in supine position, B) Duration of attacks less than 1 minute, C) Positional nystagmus elicited after a latency of few seconds by Dix-Hallpike maneuver. D) Does not attribute to any other disorder.

Exclusion criteria: Patients who had systemic diseases, neurological disorders, moderate or severe hearing loss, inflammatory diseases, any disease which affected the inflammatory biomarkers

All patients were made to undergo neurologic, otolaryngologic and audiometric tests to exclude any other diseases that may cause misdiagnosis. The healthy volunteers were selected as controls. The positional nystagmus was assessed by video-electronystagmography. Posterior canal BPPV was diagnosed in patients who had upbeat torsional, geotropic nystagmus lasting less than 30 seconds. Anterior canal BPPV was diagnosed in patients torsional down beating nystagmus. For horizontal canal BPPV, short latency of positional vertigo episodes, while supine, purely horizontal nystagmus induced by rotating the head, with greater intensity on one side, during the upright sitting position, absence of spontaneous nystagmus, unfatigable nystagmus with repeated positioning and absence of CNS disease. Before medical treatments, the blood samples were collected by careful venepuncture during emergency admission. For biochemical tests, samples were collected in EDTA tubes for haematological tests and in dry tubes. Laboratory investigations such as serum hemogram, full biochemistry profiles which includes glucose, total cholesterol, low density lipoprotein, cholesterol, HDL, SGOT, SGPT, creatinine, electrolytes, bilirubin, vitamin B12, folic acid, TSH, free T4, hsCRP and ESR were measured. A chi square test was used to analyse the significance of multiple comparison of relative frequencies between the groups. Fischer test was used when the chi square test did not meet the conditions. The statistical significance was accepted as $P<0.05$.

Statistical analysis was performed using SPSS version 22. Normality of the continuous data was checked using K.S test.

The continuous variables were described as mean ± standard deviation. The categorical variables were presented in terms of their frequencies and proportions. For comparison of means between the groups, independent t-test was used. For comparison of ratios, Mann-Whitney U test was used.

This study was approved by institutional ethics committee. An informed written consent was collected from all the patients.

Results

Table-1: Demographic characteristics of patients.

Characteristics		Controls (Mean± SD)/n%	Patients (Mean± SD)/n%
Age		36±10.8	38±13.9
Gender	Female	65 (72.2%)	70 (77.8%)
	Male	25 (27.8%)	20 (22.2%)
Smoking		10 (11.1%)	30 (33.3%)
Alcohol consumption		0 (0.0%)	2 (2.2%)

Table 1 showed that the patients were aged between 15 and 75 years. Females were higher than males in both the groups. 10 (11.1%) patients were smoking in control group and 30 (33.3%) patients were smoking in patient group. Smoking rate was higher in-patient group when compared to the control group. Alcohol consumption was 0% in control group and 2.2% in patient group.

Table-2: Clinical characteristics of patients.

Characteristics	Controls (Mean± SD)/n%	Patients (Mean± SD)/n%
Vitamin B12	325.6±250.6	251.9±155.2
WBC	7.0±2.0	7.6±2.8
Hgb	13.4±1.5	13.0±1.6
Hct	42.0±3.4	41.5±3.6
Glucose	94.2±10.1	96.6±13.0
Creatinine	0.7±0.3	0.7±0.4
Urea	28.6±8.6	25.7±6.7
Total cholesterol	198.2±35.4	192.1±41.7
Triglyceride	103.5±50.4	105.7±56.9
HDL	50.8±11.7	55.9±51.9
LDL	124.2±28.4	118.6±31.5
SGOT	19.4±4.7	23.5±11.1
SGPT	19.6±9.9	23.7±18.9
Sodium	138.5±2.8	139.8±2.4
Potassium	4.5±0.3	4.4±0.2
Chlorine	104.9±2.2	105.0±2.7
Folate	7.8±3.0	7.6±3.3
FT4	1.00±0.11	0.86±0.14
TSH	1.8±1.4	1.7±1.9
ESR	14.6±8.0	18.4±11.6

WBC-White blood cells, Hgb-Haemoglobin, Hct-Haematocrit, HDL-High density lipoprotein, LDL-Low density lipoprotein, SGOT-serum glutamic oxaloacetic transaminase, SGPT-serum glutamic pyruvic transaminase, FT4-free T4, TSH-thyroid stimulating harmone, ESR-erythrocyte sedimentation rate.

Table 2 showed that WBC, haemoglobin, glucose, total cholesterol, triglyceride, LDL, SGPT, SGOT, electrolytes, folate and TSH levels showed no significant differences. Significant lower levels were observed in BPPV patients for vitamin B12, haematocrit, creatinine, urea, fT4, lymphocyte, total, direct, indirect bilirubin levels. HDL, SGOT, ESR values were significantly higher in BPPV patients.

Table-3: Compares inflammatory biomarker levels in BPPV patients and healthy controls.

Characteristics	Controls (Mean±SD)/n%	Patients (Mean±SD)/n%
Neutrophil	4.0±1.2	4.2±1.4
PLT	258.6±51.8	255.2±53.6
Lymphocyte	2.8±0.6	2.5±0.7
Monocyte	0.6±0.3	0.7±0.4
MHR	0.0±0.0	0.0±0.0
NLR	1.5±0.6	1.8±0.7
hsCRP	0.2±0.3	0.5±0.5
PLR	104.3±36.6	116.8±41.8
MPV	10.0±1.3	10.5±0.8
Total bilirubin	0.92±0.47	0.63±0.27
Direct bilirubin	0.15±0.04	0.11±0.06
Indirect bilirubin	0.76±0.34	0.49±0.26

HsCRP-High sensitivity C-reactive protein, MHR-monocyte to HDL-C ratio, MPV-mean platelet volume, NLR-neutrophil to lymphocyte ratio, PLR-platelet to lymphocyte ratio, PLT-Platelet. Table 3 showed that the mean NLR, PLR, MPV values were higher significantly in BPPV patients when compared to healthy control patients. Neutrophil, platelet, monocyte, MHR, CRP were almost similar in both the groups.

In univariate model, vitamin B12, Hct, creatinine, urea, HDL, SGOT, fT4, ESR, lymphocyte, MPV, total bilirubin, direct bilirubin, indirect bilirubin values were significantly efficient.(p=0.030, p=0.044, p=0.000, p=0.001, p=0.047, p=0.020, p=0.000, p=0.007, p=0.019, p=0.018, p=0.000, p=0.000, p=0.000) respectively.

In multivariate model, there was significant difference in patient group for serum creatinine, SGOT, fT4, MPV, total bilirubin, indirect bilirubin. (p=0.001, p=0.021, p=0.000, p=0.011, p=0.015, p=0.004) respectively.

Discussion

In the present study, the preliminary results showed that pathogenesis of BPPV is connected to inflammation. Compared to healthy volunteers, NLR, PLR, MPV and ESR were significantly higher and bilirubin levels were lower in BPPV patients. In elderly and in women, incidence of BPPV is higher. In the present study, BPPV was higher in women. The most common cause of BPPV is infection, trauma, ear operations, ototoxicity, in majority of patients, it was idiopathic in the present study.

It has been reported that the median duration of an episode of BPPV is around 2 weeks as per the study by Von Brevern M et al [1]. They also found these patients to have significant positive association with hypertension, dyslipidemia and stroke. The present study excluded patients with coexisting metabolic illness such as Diabetes, hypertension and dyslipidemia. This study was the first to investigate NLR exclusively in BPPV patients. Role of NLR as a biomarker in inflammatory conditions such as autoimmune diseases, Diabetes and malignancies has been evaluated before. However, underlying inflammation during an acute attack of BPPV has not been previously evaluated.

In a study conducted by Tekesin A et al it was reported that the laboratory investigations conducted included serum hemogram, full biochemistry profiles, vitamin levels, thyroid hormone profiles, high sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR) [6]. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte to HDL-cholesterol ratio (MHR) values were calculated and compared between the patients and healthy subjects. The mean age was 39.1±12.4 years for patients, and 37.0±11.9 for controls.

Vitamin B12, hematocrit (Hct), creatinine, urea, and fT4 values, lymphocyte, total bilirubin, direct bilirubin and indirect bilirubin levels were significantly lower in BPPV patients ($p < 0.05$), while HDL, SGOT, and ESR values were significantly higher. In the BPPV patients the mean NLR, PLR, and mean platelet volume (MPV) values were significantly higher than in the control subjects.

Neutrophil, platelet, monocyte, MHR, and CRP values were similar in both groups ($p > 0.05$) which was similar to the present study. Yuan J et al reported that serum uric acid (SUA) [279.0±84.7 vs. 331.0±82.7], hemoglobin A1C (HbA1c) [5.75±1.17 vs. 6.61±1.00], albumin [38.1±3.71 vs. 40.9±4.1], and creatinine [68.4±19.3 vs. 81.5±24.1] were significantly lower in patients with BPPV compared with controls (P<0.05) [7]. Multiple logistic regression analysis showed that lower levels of HbA1c and albumin were independently associated with BPPV (P<0.05), with odds ratio (OR) 0.680 (95% CI 0.551-0.839) and 0.338 (95% CI 0.190-0.603), respectively. However, the level of SUA was not independently related with BPPV [OR=0.999 (95% CI 0.991-1.006), P=0.713]. There were no significant differences between the parameters of systolic blood pressure, diastolic blood pressure, blood routine examination, lipid profiles, homocysteine, pre-albumin, and blood urea nitrogen in patients with BPPV vs. controls (P>0.05).

Xinglong Yang et al conducted a study in which A total of 12 studies were included in the analysis. There was a strong tendency for serum uric acid levels to be associated with risk of BPPV among studies conducted in China (OR 0.69, 95%CI 0.01–1.40, p= 0.053), but not among studies outside China (OR 1.07, 95%CI 1.08–3.22, p= 0.33) [8]. Across all studies, serum uric acid level was significantly higher among individuals with BPPV than among controls (OR 0.78, 95% CI 0.15–1.41, p= 0.015), yet it did not independently predict risk of the disorder (OR 1.003, 95%CI 0.995–1.012, p= 0.471).

Chen CC et al reported that 31.2% of BPPV cases had a CND. The most common associated CNDs were cerebrovascular disease and migraines [9]. The two groups showed similar age distributions, canal involvement, success rates of repositioning, and cycles of treatment used to achieve complete resolution. The major differences were the proportion of females (89.7%) and a right-side predominance (75.9%) in the CND group.

There was a trend of more residual dizziness (RD) after successful repositioning in the CND group, but the difference was not significant. The reason for the female and right-side predominance in the CND group is unclear. Celikbilek A et al concluded that the lipid profiles and SUA levels were higher in patients with BPPV than detected in controls ($P < 0.05$ and $P < 0.001$, respectively).

Albumin and SUA values were independently associated with BPPV in multiple logistic regression models ($P < 0.05$ and $P < 0.001$, respectively) [10]. A cutoff value of 4 for SUA level with a sensitivity of 0.72 (0.58-0.84) and a specificity of 0.60 (0.43-0.75) was obtained in the receiver operating characteristic analyses. There was a significant decrement in SUA level 1 month after the vertigo attack compared with the values obtained during the attack ($P < 0.001$). Among the most involved type of BPPV (PSC BPPV), the right side was affected in 26 patients (57.8%) and the left side in 19 patients (42.2%). SUA levels did not differ statistically in patients with PSC BPPV for either the right or left sides ($P > 0.05$) [11,12].

According to Sahin C et al the NLR in patients of peripheral vertigo was elevated during admissions and it declined at the time of discharge [13]. The mean NLR baseline in healthy adults in China was 1.5 ± 0.05 and a study from Chennai, India reported NLR of 1.5 ± 0.41 among healthy non-diabetic individuals [14,15]. The median absolute neutrophil and absolute lymphocyte counts were 4742.08 ± 1853.7, 1767.06 ± 821.4 respectively, and the median (Inter Quartile Range) of NLR was 2.3 (1.5,4.2). Thus, this could possibly explain an underlying inflammation in patients with BPPV in the present study population. Intense research is very much needed with comparison to control groups in order to derive evidences for the exact link of BPPV with elevated NLR.

Studies have reported high NLR values, indicating increased mortality rates in colorectal, hepatocellular, gastric, and endocrine malignancies [11,12,13,14]. Liu et al. compared the outcomes in 159 patients with malignant thyroid nodules and 318 patients with benign nodules and reported a correlation between high preoperative NLR values and the tumor size and prognosis [15]. Many hypotheses have been proposed to explain this situation.

Neutrophilia and/or lymphopenia have been accepted as indicators of increased NLR and inflammation. It has been demonstrated that the cytolytic activities of natural killer cells and lymphocytes have been inhibited with the increase in the neutrophil count and, therefore, neutrophil infiltration into tumor tissue has been accepted as an indicator of poor prognosis [16,17].

Inflammatory cytokines and chemokines, as well as neutrophils, are produced by the tumor cells. Neutrophils and other immune system cells secrete tumor growth-promoting factors, such as vascular endothelial growth factor, hepatocyte growth factor, interleukin 6, and interleukin 8, and the growth of tumor cells is stimulated. Therefore, increased NLR and interleukin levels are accompanied by peritumoral macrophage infiltration and this indicates a poor prognosis [18].

Limitations

Large scale studies disclosing the role of ESR, Mean Platelet Volume, Platelet-Lymphocyte Ratio, Monocyte-HDL Ratio or CRP and comparing with NLR in BPPV has to be carried out as these economical parameters could be used at resource limited settings in order to provide a better quality of care for the patients.

Conclusion

This study suggests that the potential biomarkers of BPPV were NLR, PLR, MPV, ESR and bilirubin levels as these biomarkers are available widely and they are an addition to theory of inflammation, and they are inexpensive.

What the study adds to the existing knowledge?

Further detailed follow up studies where NLR in BPPV is calculated before and after an attack is warranted. Evaluating the role of anti-inflammatory medications as a possible adjuvant treatment option for BPPV needs to be considered.

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