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HIGH SENSITIVITY CRP IN FEMALE PATIENTS WITH ISCHEMIC STROKE, EPILEPSY, POST-STROKE EPILEPSY AND ISCHEMIC HEART DISEASE

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ABSTRACT

Estimation of C-reactive protein (CRP) is widely considered for investigating the degree of inflammation especially in coronary heart disease (CHD) and ischemic stroke (IS). A variety of studies have been conducted. However, precise correlation of age-related hs-CRP levels with the severity of injury is not known. Hence, we carried out present study in age-matched (age range 55-66 years) female patients of ischemic stroke (IS), epilepsy (E), post-ischemic stroke epilepsy (pIS-E) and ischemic heart disease (IHD) and compared with the normal female control subjects (C). Group comparisons showed significant variations of hs-CRP (mg/L) for IS vs. C, E vs. C, pIS-E vs. C, IHD vs. C, IHD vs. E, E vs. IS and IHD vs. pIS-E and non-significant change for pIS-E vs. IS, IHD vs. IS and pIS-E vs. E, that revealed the role inflammation via change in hs-CRP not only in patients with ischemic disorders but also in epilepsy patients though the extent of increase in hs-CRP was quite less in epilepsy patients. Moreover, significant positive correlation of age and hs-CRP levels was revealed for the mentioned female patients with ischemic disorders and epilepsy. Conclusively, we investigated the role and involvement of hs-CRP in female patients with ischemic stroke, ischemic heart disease and post-ischemic stroke epilepsy and also in patients with epilepsy without apparent involvement of ischemic complications. Hence, inflammation seems a major factor causing atherosclerotic conditions in neurovascular and cardiovascular disorders.

Keywords: hs-CRP, age, inflammation, ischemic stroke, epilepsy, post-ischemic stroke epilepsy, ischemic heart disease

INTRODUCTION

Estimation of C-reactive protein (CRP) is widely suggested for investigating the degree of inflammation (Gabay and Kushner, 1999) and is considered as a marker of acute and chronic inflammation (Danesh *et al*., 2004), especially in coronary artery disease (CAD) and ischemic stroke (Matsuo *et al*., 2016; Oemrawsingh *et al*., 2016). Furthermore, it has been revealed that high sensitivity CRP (hs-CRP) is helpful in predicting stroke, ischemic heart disease and other disorders in young and elder men and women. It was found that hs-CRP levels may also serve as predictor in healthy people for a possibility of their cardiac complications in future (Koenig *et al*., 1999). However, precise correlation of hs-CRP levels with the severity of injury is not known.

It was shown that atherosclerosis is not developed only by dyslipidemia (Paramsothy *et al*., 2010) but also associated much with inflammation via plague complexity and instability (Lombardo *et al*., 2004). Hence, CRP the indicator of systemic inflammation is helpful in predicting atherosclerosis (Khera *et al*., 2006). Association of CRP with increasing risk of stroke mainly ischemic stroke have been revealed, though there are other investigations not showing precise association (Bos *et al*., 2006).

The epileptogenesis mechanisms at cellular and molecular level are not clear yet. However, the role of inflammation (focal or systemic) is known to cause hyper-excitability in neuronal networks, and hence, mediates the occurrence of epilepsy (Musto *et al*., 2016). Recent studies emphasize more on the association of the development of epilepsy and inflammation (Hussain, 2010; Paudel *et al*., 2018; Terrone *et al*., 2019). However, relevant studies to CRP in epilepsy show controversial results. Some studies investigated significant association relationship for hs-CRP versus epilepsy, though not confirmed in other reports. Hence, the current study was planned to compare CRP in epilepsy subjects against normal controls considering the possible involvement of age.

Increased levels of hs-CRP were revealed associated with post-stroke epilepsy (Di Napoli *et al*., 2018). It has been documented that after occurrence of first seizure, development of recurrent seizures and increased fatality may

occur and epilepsy may occur after stroke with the prevalence range from 6.3% to 12.4% (Liu *et al*., 2012; Yang *et al*., 2014) .

The hs-CRP and cardiovascular risks have been discussed in detail and even small increase in the level of hs-CRP in view of its high sensitivity serves as an indicator for predicting complications and diseased conditions especially related to ischemic heart disease. The hs-CRP elevates in patients with increasing severity in ischemic heart disease (Hussain, 1991; Mahmood *et al*., 1998; Kincl *et al*., 2010; Koc *et al*., 2010; Harutyunyan *et al*., 2011). However, controversial results for the role of hs-CRP in cardiac ischemic disorders have also been obtained (Harutyunyan *et al*., 2011; Rashidinejad et *al*., 2013). Membrane self-assembly studies reveal the subtle alterations clarifying these studies (Ahmadi *et al*., 2017). One report shows hs-CRP levels associated to CHD (coronary heart disease) but not to the severity of CHD though CRP was not associated to the levels of hs-CRP in normal subjects and individuals with higher risk of ischemic disorders (Rashidinejad *et al*., 2013).

Increase in the level of hs-CRP was obtained small-artery occlusion leading to ischemic stroke only in younger patients and not in older subjects (Qiu *et al*., 2016) that seemed the effect of aging leading to weakening of innate as well as adaptive immunity (Gao *et al*., 2014). Other reports investigated that increased age might be one major risk factor in ischemic stroke (Wada *et al*., 2008; Lavallée *et al*., 2013). Hs-CRP in female subjects having ischemic stroke and at 3 months post-stroke were found elevated (Åberg *et al*., 2020). Higher hs-CRP levels were found as prediction for progressive motor deficit deterioration (PMD) with penetrating artery infarction (PAI) (Gong *et al*., 2019).

Significant increase in peripheral blood CRP for epilepsy patients against healthy control subjects was found in adult subjects but not in children (Zhong *et al*., 2019). The results compared with age/gender- matched young adults and normal children controls showed marked increase in CRP and other markers in patients with epilepsy (Meguid *et al*., 2018). Another study reveals that age and gender matched young epilepsy patients presented no significant difference of hs-CRP for those diagnosed newly against valproic acid treated patients (Nisha *et al*., 2018).

Age matched epilepsy patients compared with healthy subjects to evaluate atherosclerotic retinopathy and neuropathy for the risk of macroangiopathy revealed increased hs-CRP and other inflammatory markers (Chen *et al*., 2018). A comparative inflammatory process was studied in patients after surgery for temporal lobe epilepsy that showed excessively elevated hs-CRP in these patients without infection (Woernle *et al*., 2013).

One old person having stroke previously and later experiencing epileptic seizures presented elevated hs-CRP levels, indicating systemic inflammation in post-stroke epilepsy (Matsuo *et al*., 2014). Another study found that the stroke patients having epilepsy seizures and other discomforts were mostly the young subjects whereas elevated hs-CRP levels were found mostly in older subjects (Kes *et al*., 2016).

Male and female patients with ischemic heart disease indicated various inflammatory and behavioral mechanisms with even small associations of hs-CRP and other markers (Mommersteeg *et al*., 2019). Patients with SIHD (stable form of ischemic heart disease) under DAPT (dual-antiplatelet-therapy) showed increased hs-CRP (Golukhova *et al*., 2018). The hs-CRP estimated in men showed increase in the development of venous thromboembolism (VTE) with a linear association (Kunutsor *et al*., 2017). Increased hs-CRP were obtained though not related to IHD severity in patients of mean age 60.3 years (Bouzidi *et al*., 2020).

Furthermore, most of the studies related to CRP in ischemic disorders were carried out in Europe and America and when compared it was found that levels of CRP were higher in Asians compared to European people (Chambers *et al*., 2001). In view of this reason, we planned to assess the levels of has-CRP in the local population. However, our major aim was to have idea whether patients with ischemic disorders without obesity or over-weight may have high hs-CRP levels. This information was also essential to verify that ischemic disorders and atherosclerosis may also occur due to dysfunction in inflammatory disorders manifesting change in the levels of inflammatory markers including hs-CRP besides occurring due to dyslipidemia.

MATERIALS AND METHODS

The present study comprised female ischemic stroke patients (IS, n: 26, mean age: 60.42 years), epilepsy (E, n: 25, mean age:60.44 years), post-ischemic stroke epilepsy (pIS-E, n: 19, mean age: 60.68 years) and ischemic heart disease (IHD, n: 26, mean age: 60.65 years), along with normal female control subjects (C, n: 25, mean age: 60.56 years).

The above mentioned patients with ischemic disorders and epilepsy were first diagnosed properly with the help of their clinical manifestations as well as biochemical/physiological assessments, and differential diagnosis. Proper diagnosis needed family and medical history of the patients and thorough examination including physical check up and performing diagnostic/biochemical tests. In that regard, expert clinicians helped in diagnosing the patients with

ischemic disorders and epilepsy. A variety of tests including clinical, neurological, biochemical, physiological, radiographic, ultrasound and nuclear imaging diagnostic tests were found helpful for diagnostic purpose.

The present study contains the data of female subjects without obesity and without over-weight/ under-weight status confirmed by BMI. The clinical, physiological and biochemical study of these subjects/ patients was done thoroughly. The venepuncture in ethical perspectives is a minimally invasive method used frequently as part of the investigation procedure. However, the patients were told about the purpose and benefits of present study.. After taking consent, blood was withdrawn and managed. The blood sample drawn was centrifuged quickly and serum separated for the analysis of hs-CRP levels (mg/L) using the standard methods.

The hs-CRP serum levels were determined, recorded as mean ± SD t (df) and p values (using unpaired t test) were analyzed statistically. Employing the general statistical principles (Zahir *et al*., 2014), each group of patients and normal control subjects were separately tested for age and hs-CRP levels by one sample t test by using hypothetical mean for predicting the dispersion pattern of each single group values with the determination of t (df) and two tailed p values to have idea of any discrepancies in the data.

For determining the association of age and the levels of hs-CRP, values of slope, intercept, R^2 and p values for the regression lines were obtained. Spreadsheets (written for Excel; workable with Calc program) were found helpful for analyzing the data. Using spreadsheets was easy compared to statistical analysis in other programs. The Y intercept, regression coefficient, the R^2 value, degree of freedom, the P value and Y estimator and an X estimator were obtained with the help of spreadsheets. Serum levels of hs-CRP were determined in age-matched normal healthy female control subjects as well. These controls served for comparing the results of the patients with ischemic disorders studied in the present report.

RESULTS

The serum levels (mean ± SD) of hs-CRP (mg/L) are shown in Fig.1 for normal healthy female subjects (C; 0.97±0.63) and female patients with ischemic stroke (IS; 4.41±2.49), epilepsy (E; 2.76±1.85), post-ischemic stroke epilepsy (pIS-E; 3.31±2.19) and ischemic heart disease (IHD; 5.33±2.81). Analysis of the data indicated highly significant variations ($p < 0.0001$) for IS vs. C, E vs. C, pIS-E vs. C, IHD vs. C and IHD vs. E, very significant change (=0.0100) for E vs. IS; significant variation (=0.0126) for IHD vs. pIS-E; and non-significant change ($p>0.05$) for pIS-E vs. IS, IHD vs. IS and pIS-E vs. E.

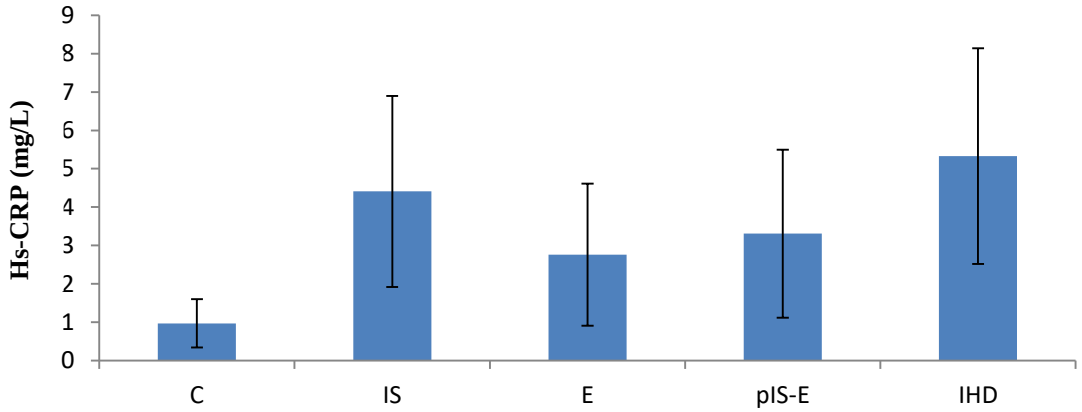

Fig.1. Serum hs-CRP levels in female patients with ischemic stroke, epilepsy, post- ischemic stroke epilepsy and ischemic heart disease.

Values of hs-CRP are mean ±SD; C: Normal female control subjects; IS: Female patients with ischemic stroke; E: Female patients with epilepsy; pIS-E: Female patients with post-ischemic stroke epilepsy; IHD: Female patients with ischemic heart disease; Highly significant p values ($p<0.0001$) for IS vs. C, E vs. C, pIS-E vs. C, IHD vs. C and IHD vs. E; very significant p value (=0.0100) for E vs. IS; significant p values (=0.0126) for IHD vs. pIS-E; and non-significant p values (p.>.0.05) for pIS-E vs. IS, IHD vs. IS and pIS-E vs. E

All four groups of patients with ischemic disorders and epilepsy compared to normal controls showed significantly or highly significantly increase in hs-CRP levels, which revealed the role of inflammation not only in ischemic disorders but also in epileptic disorders though the extent of increase in hs-CRP was quite less in epilepsy

patients. This was evident while comparing the hs-CRP levels for E vs IS (quite significant) but comparing pIS-E vs. IS and pIS-E vs. E did not show significant change ($p>0.05$). Hence, the extent of involvement of inflammation seems significantly high in patients with IS or IHD.

The second part of our work was related to assessing the association of the age of subjects (C, IS, E, pIS-E and IHD) and their respective serum hs-CRP levels (Fig 2-6).

Plot between the age of normal female control subjects (C) and their serum hs-CRP levels showed a linear relationship with the slope value of 0.09 and R^2 as 0.2576 ($p<0.01$; Fig.2). Range of the age of subjects in the present study was quite limited (55-66 years). However, it revealed positive correlation of serum hs-CRP levels with the increasing age of normal female control subjects from 55 years onward to 66 years. This indicates that aging subjects in general have stressful conditions leading to inflammation manifested in the form of inflammatory markers including hs-CRP.

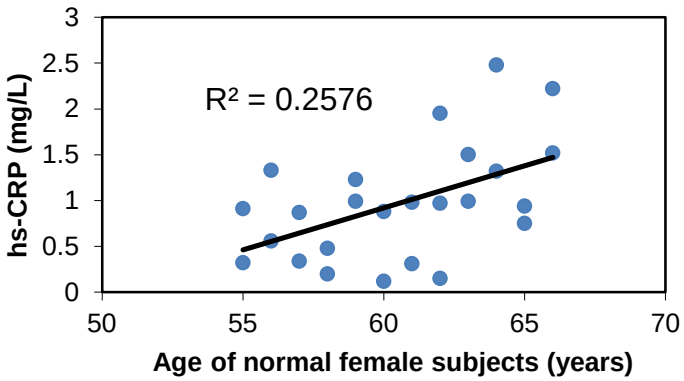

Fig.2. Association of the age and serum hs-CRP in normal female control subjects.

Linear relationship was obtained for age and serum hs-CRP in female patients with ischemic stroke (IS) that showed the slope value of 0.42 and R^2 as 0.35 ($p<0.001$; Fig.3). It indicated that the positive linear relationship was quite high as compared to that found in normal female control subjects (C). Increased positive linear relationship as compared to that in normal female control subjects (C) reveals increased manifestation of inflammation in the form of elevated serum hs-CRP level.

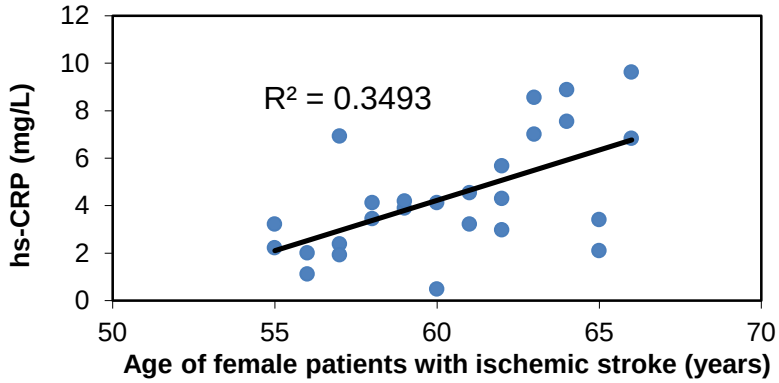

Fig.3. Association of the age and serum hs-CRP in female patients with ischemic stroke.

Age and serum hs-CRP in female patients with epilepsy (E) were plotted that showed positive linear relationship (slope value of 0.34; R^2 as 0.41 ($p<0.0005$; Fig.4). This showed that the positive linear relationship and 0.41 slope value were quite high as compared to those found in normal female control subjects (C).

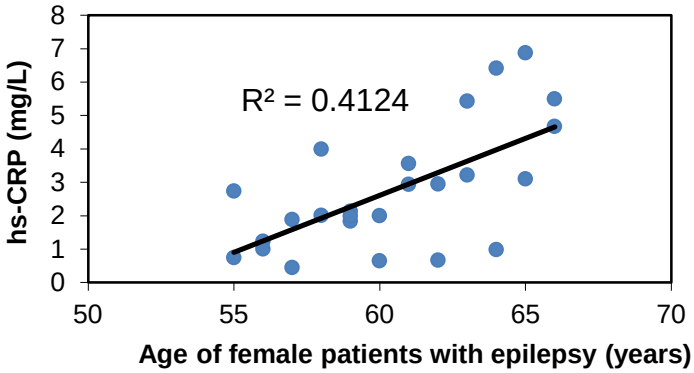

Fig.4. Association of the age and serum hs-CRP in female patients with epilepsy.

Linear regression for the age and serum hs-CRP of the female patients with post-ischemic stroke epilepsy (pIS-E) gave a positive linear correlation (slope value of 0.30 and R^2 as 0.25 ($p<0.028$; Fig.4). Beside positive correlation, the level of correlation was different from both the patients with ischemic stroke (IS) and patients with epilepsy (E) and normal controls (C) as well. This is shown in Fig.1.

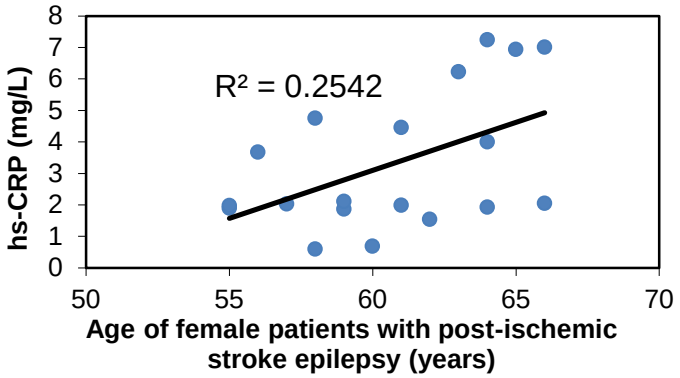

Fig.5. Association of the age and serum hs-CRP in female patients with post-ischemic stroke epilepsy.

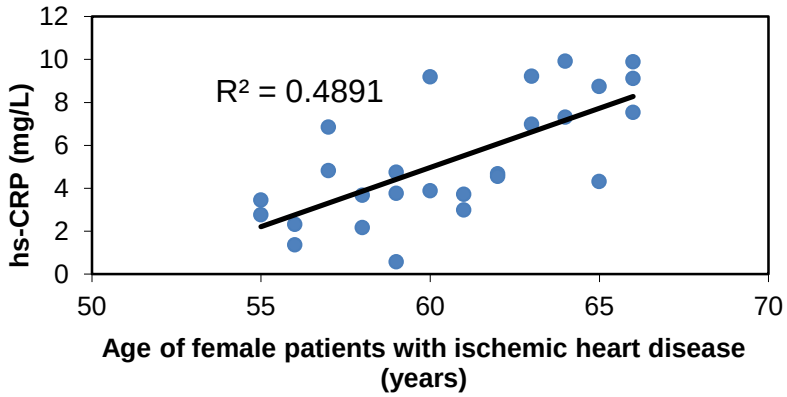

Fig.6. Association of the age and serum hs-CRP in female patients with ischemic heart disease.

Linear regression obtained for the age and serum hs-CRP of the female patients with ischemic heart disease (IHD) showed a positive linear correlation (slope value of 0.55 and R^2 as 0.49 ($p<0.00007$; Fig.5). Patients in this group revealed higher positive correlation as well as higher level of correlation (shown by slope value in Fig 5 and hs-CRP level shown in Fig.1) as compared to those in patients with ischemic stroke (IS), epilepsy (E), post-ischemic stroke epilepsy (pIS-E), and normal controls (C) manifesting increased inflammation in the form of elevated serum hs-CRP level in these patients.

For summing up the results by combining the results shown in Fig. 1 and Fig.2-5, slope values for patient groups and normal controls were compared that indicated the extent of serum hs-CRP levels in descending order as: IHD (0.55) > IS (0.42)> E (0.34)> pIS-E (0.30)>C (0.09).

DISCUSSION

Main purpose of carrying out present study was to investigate the extent of inflammation in ischemic heart disease and ischemic stroke as has been suggested previously (Lombardo *et al*., 2004) since dyslipidemia is not the sole cause of atherosclerosis (Paramsothy *et al*., 2010). Hence, we were interested to investigate that CRP serving as an indicator of systemic inflammation is helpful in predicting atherosclerosis (Khera *et al*., 2006). Our other main target in present work was to find the correlation and the extent of correlation of age with serum levels of hs-CRP in female patients mainly having ischemic disorders.

The female patients with ischemic disorders in the present study were not obese or over-weight/ under-weight but still showed significant increase in serum hs-CRP levels with the increase in age. Estimation of hs-CRP in normal healthy female patients was included in the study for comparing the level of hs-CRP and hence the inflammatory status in ischemic patients. However, it was also in our consideration that the estimation of hs-CRP levels in normal subjects may also serve as predictor in healthy people for a possibility of their ischemic/ cardiac complications in future (Koenig *et al*., 1999).

Involvement of hs-CRP in patients with ischemic disorders in the present report has been investigated that is in accordance with the existing information about the important role of hs-CRP in inflammation and degree of inflammation (Gabay and Kushner, 1999; Danesh *et al*., 2004; Hussain *et al*., 2007; Sohail *et al*., 2013; Matsuo *et al*., 2016; Oemrawsingh *et al*., 2016) in both young and elder men and women.

Our results for serum hs-CRP in women with post-ischemic stroke are similar to another study where increased CRP levels associated with post-stroke epilepsy (Di Napoli *et al*., 2018). The present results can further be explained with a previous study that shows that after the occurrence of first seizure, development of recurrent seizures increased fatality and epilepsy occurred after stroke with the prevalence range from 6.3% to 12.4% (Liu *et al*., 2012; Yang *et al*., 2014). Controversial results for the role of hs-CRP in cardiac ischemic disorders were obtained (Kincl *et al*., 2010; Rashidinejad *et al*., 2013). However, our results are similar to some of the reports (Kincl *et al*., 2010; Koc *et al*., 2010; Harutyunyan *et al*., 2011).

It seems not easy to interpret the present data of female patients with ischemic stroke and ischemic heart disease in view of quite limited age range. However, it was found that aging increased hs-CRP levels in patients with small-artery occlusion (SAO) leading to ischemic stroke, but only in younger, not in older patients (Qiu *et al*., 2016), and it was predicted that it occurred due to aging that has an association with decreased adaptive as well as innate immunity (Gao *et al*., 2014). However, our data though with limited age range shows similar status for inflammation as described by Gao *et al*. (2014) and other investigators (Wada *et al*., 2008; Lavallée *et al*., 2013). Other reports having similar age range of the patients with ischemic stroke showed similar pattern of increased hs-CRP levels (Gong *et al*., 2019; Åberg *et al*., 2020). But we suggest for further studies involving wider age range data for precise clarification of involvement of inflammatory factors including hs-CRP in atherosclerotic conditions of coronary artery disease and ischemic stroke.

Highly significant elevations of serum hs-CRP in patients with ischemic stroke in our present report resemble with several of the previous investigations (Lombardo *et al*., 2004; Khera *et al*., 2006) though vary from other reports (Bos *et al*., 2006) since we studied only female patients with a small age range.

The relationship of CRP and epilepsy has not been studied precisely. Hence, the present study was planned to compare the CRP levels in epilepsy patients with the healthy controls considering the possible involvement of age. The serum levels of hs-CRP for epilepsy and post-ischemic stroke epilepsy investigated in the current study can be interpreted with the mechanisms of epileptogenesis emphasizing the role of inflammation (focal or systemic) in causing influence on hyper-excitability of neuronal networks, and hence, mediating the onset of epilepsy (Musto *et al*., 2016; Paudel *et al*., 2018; Terrone *et al*., 2019).

The results for the adult patients with epilepsy showing significant increase in peripheral blood CRP and indicating association between epilepsy and inflammation in adults (Woernle *et al*., 2013; Chen *et al*., 2018; Zhong *et al*., 2019) are similar to our results in the present study. Age and sex based study in patients with epilepsy (Meguid *et al*., 2018) indicating marked increase in CRP also verifies our present results. Increased hs-CRP in our present report are also similar to previous reports of post-stroke epilepsy presenting elevated CRP levels in older patients indicating systemic inflammation (Matsuo *et al*., 2014; Kes *et al*., 2016).

Elevated hs-CRP investigated in patients with ischemic heart disease (Kunutsor *et al*., 2017; Golukhova *et al*., 2018; Mommersteeg *et al*., 2019; Bouzidi *et al*., 2020) are quite similar to our present results in female patients with

ischemic heart disease. These reports and our present study explain the involvement of hs-CRP in atherosclerotic process in coronary artery disease and related disorders.

Conclusively, we investigated the role and involvement of hs-CRP in female patients with ischemic stroke, ischemic heart disease and post-ischemic stroke epilepsy and also in patients with epilepsy without apparent involvement of ischemic complications. Hence, inflammation seems a major factor causing atherosclerotic conditions in neurovascular and cardiovascular disorders.

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