SERUM C-REACTIVE PROTEIN AS INFLAMMATORY MARKER IN MEN WITH EPILEPSY

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ABSTRACT

It is well known that inflammation may lead to the development of quite complex human diseases. One important marker for investigating the degree of inflammation is C-reactive protein (CRP) for both acute and chronic types of inflammation. There are studies that show the association of CRP with epilepsy. However, other studies contradict such an association. Hence, the present work was conducted to evaluate and compare the age-based CRP levels in epilepsy male subjects vs. healthy male controls to verify the involvement of CRP in non-obese men with epilepsy. A total number of 25 male epilepsy (EP) subjects and 25 normal male control (C) subjects were consulted in the present study. The serum levels of hs-CRP were determined using the standard method of the immunoturbidimetric assay (Behring-Nephelometer: BNA-2, Siemens USA). The serum CRP in male subjects with epilepsy compared to male control subjects showed a highly significant increase in epilepsy subjects (P value < 0.0001). The plot between age and serum CRP in male control subjects showed a non-significant positive linear correlation. The age (years) plotted against serum CRP in male subjects with epilepsy showed a highly significant positive linear correlation (R2: 0.41; P: 0.0004). The present study helps understand the role of CRP and the association of CRP with inflammation causing epileptogenesis via molecular and cellular mechanisms. However, further wider age-range-based studies may confirm the precise role of CRP in epilepsy involving ischemic/ inflammatory disorders.

Key Words: Epilepsy, C-reactive protein (CRP), inflammation, inflammatory marker, age-based CRP levels

INTRODUCTION

It is well known that inflammation may lead to the development of quite complex human diseases (Sohail *et al.*, 2013; Gupta *et al.*, 2018; Ligthart *et al.*, 2018; Haider Kazmi *et al.*, 2022). One important marker for investigating the degree of inflammation is C-reactive protein (CRP) (Mahmood *et al.*, 1998; Gabay and Kushner, 1999; Hussain *et al.*, 2007), for both acute and chronic types of inflammation (Danesh *et al.*, 2004; Zhang *et al.*, 2019). Furthermore, it has been revealed that high sensitivity CRP (hs-CRP) is a main acute-phase reactant especially for low grade chronic inflammation (Jung *et al.*, 2020) helpful as a risk factor in predicting various discomforts/ diseases in young/elder men as well as women (Rhodes *et al.*, 2010; Libby, 2012; Wang *et al.*, 2013; Khandaker *et al.*, 2015; Tao *et al.*, 2018; Jung *et al*., 2020; Markozannes *et al.*, 2021). However, relationship between the severity of injury and CRP could not be determined precisely.

The blood CRP levels were found high in rats, even quite after the status epilepticus ends (Holtman *et al.*, 2013; Gouveia *et al.*, 2015). It explains that the inflammation either focal or systemic causes neural connectivity and hyper-excitability that leads to epilepsy (Musto *et al.*, 2016; Pohlentz *et al.*, 2022). Furthermore, it has been noticed that there exists an association between inflammation and the development of epilepsy (Hussain, 2010; Paudel *et al*., 2018; Terrone *et al*., 2019).

Increased levels of high-sensitivity CRP (hs-CRP) in epilepsy patients compared to control subjects were investigated with the implication of hs-CRP in atherosclerosis (Talaat *et al.*, 2015). Another investigation revealed elevated hs-CRP levels and other inflammatory markers in age-matched epilepsy patients for determining atherosclerotic retinopathy and neuropathy for the possibility of having microangiopathy (Chen *et al.*, 2018). Highly increased hs-CRP levels were noted in an inflammatory process in patients after surgery for temporal lobe epilepsy but without infection (Woernle *et al.*, 2013).

Research carried out on children and older people having stroke and epilepsy shows that hs-CRP elevates only in older subjects (Kes *et al.*, 2016; Meguid *et al.*, 2018; Zhong *et al.*, 2019). Age and gender-matched young epilepsy patients did not present any significant variation of hs-CRP for newly diagnosed compared to valproic acid (VPA) treated patients (Nisha *et al.*, 2018). Systemic inflammation in cardiovascular disorders (Hussain, 1991) and post-stroke epilepsy manifests an increase in hs-CRP levels (Matsuo *et al*., 2014). Additionally, post-stroke epilepsy patients were found to have elevated levels of hs-CRP (Liu *et al.*, 2012; Yang *et al.*, 2014; Di Napoli *et al.*, 2018).

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How epileptogenesis occurs is still not obvious. Some studies show the association of CRP with epilepsy. However, other studies contradict such an association. The current work was hence, conducted to evaluate and compare the age-based CRP levels in epilepsy subjects vs. healthy control subjects. The main purpose/objective of the present study was to verify the involvement of CRP in normal healthy non-obese men and to predict that ischemic involvements in epilepsy may be due to inflammatory disorders via inflammatory markers mainly including CRP besides dyslipidemia.

MATERIALS AND METHODS

The total number of 25 male epilepsy (EP) subjects and 25 normal male control (C) subjects were consulted in the present study. The age range of the subjects in both groups was 55-66 years. Diagnosis and differential diagnosis of the epilepsy subjects was carried out with the general clinical neurological examination and laboratory tests. The family and medication details of the patients were recorded in a Questionnaire. The consent of epilepsy (EP) subjects and normal healthy controls (C) was obtained prior to the start of collecting subjective and objective data.

All subjects, whether patients or controls had normal weight range. This was confirmed by calculating the body mass index (BMI). The overweight and obese subjects were not included in the present study. Patients' history and blood collection were taken and blood was centrifuged. The serum levels of hs-CRP were determined using the standard method of the immunoturbidimetric assay (Behring-Nephelometer: BNA-2, Siemens USA).

The hs-CRP serum levels (mean ± SD) were determined for epilepsy patients and normal controls and compared statistically employing t-test. The statistical methods were applied considering the general statistical principles (Zahir *et al.,* 2014). The epilepsy group and control group subjects were then compared for their respective age against hs-CRP. The association of age and serum hs-CRP was determined with the help of coefficient of determination R^2 and P values obtained from the regression lines, using GraphPad Prism (version 6.0) software, San Diego, CA, USA. The minimum level of significance was considered the value of $p< 0.05$.

RESULTS

The mean age (years) in male subjects with epilepsy and male control subjects was respectively as 60.65 ±3.57 and 60.77±3.56, that showed no significant difference. The serum C-reactive protein (mg/L) in male subjects with epilepsy and male control subjects was 3.20 ± 1.94 and 1.20 ± 0.70, respectively, that showed highly significant difference (t = 4.93; df: 50; P value < 0.0001).

Association of age and serum CRP in male control subjects:

The plot between age and serum CRP in male control subjects showed non-significant positive linear correlation (R^2: 0.082; P: 0.156; Fig.1).

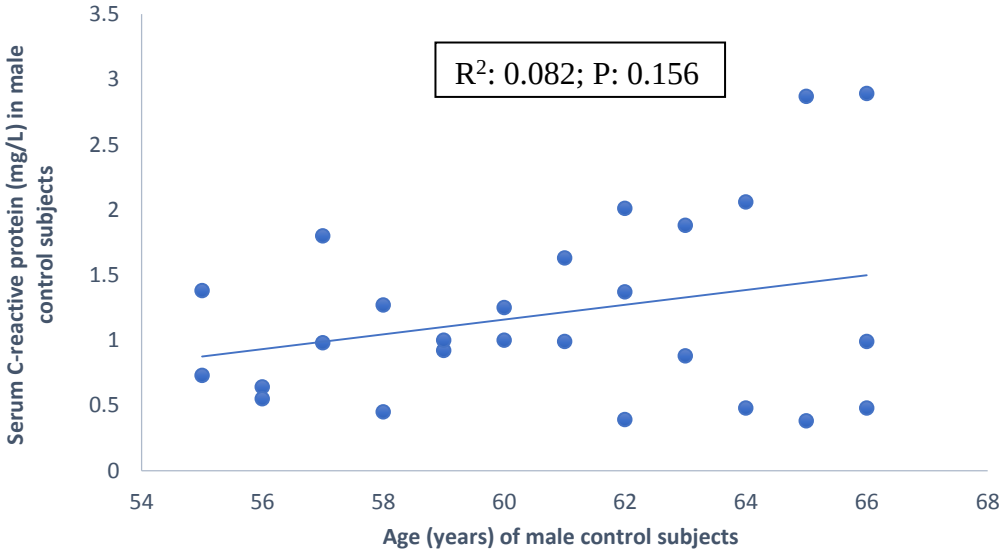

Fig.1. Association of age and serum CRP in male control subjects.

Association of age and serum CRP in male subjects with epilepsy:

The age (years) plotted against serum CRP in male subjects with epilepsy showed highly significant positive linear correlation (R^2: 0.41; P: 0.0004; Fig.2). The corresponding equation is: y = 0.3503x – 18.043.

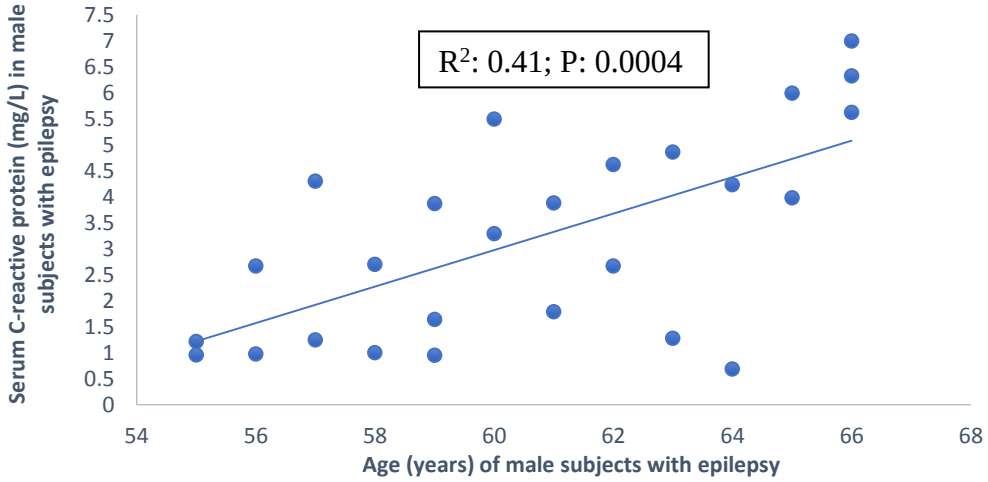

Fig.2. Association of age and serum CRP in male subjects with epilepsy.

DISCUSSION

Quite a little number of studies were conducted to understand the involvement of CRP in epilepsies. Given this, the current work was carried out especially considering the age based-variations. Epilepsy after ischemic involvement shows an association with CRP levels (Di Napoli *et al*., 2018; Si *et al*., 2021), and development of acute symptomatic seizures (Khedr *et al.,* 2021), and recurrent seizures (Moosavi *et al.,* 2016) leading in some cases to fatality (Liu *et al*., 2012; Yang *et al.,* 2014).

The present investigation emphasizes the influence of aging as the CRP significantly increased with age, though the determination of CRP in normal healthy subjects may serve as the predicting factor or a marker in healthy individuals for the future possibility of having ischemic/ inflammatory conditions (Koenig *et al*., 1999; Tang *et al.,* 2017), that is considered to occur due to inflammation (Ligthart *et al.,* 2018) and associated CRP levels (Tang *et al*., 2017). Age-related CRP elevations were viewed due to the role of CRP not only as an inflammatory marker but also as a risk factor for several aging-related disorders (Tang *et al.,* 2017).

It is known that dyslipidemia causes inflammation. However, the extent of systemic inflammation depends on other factors as well. e.g. the inflammatory factors/ markers mainly including CRP (a main acute-phase reactant for low-grade chronic inflammation) (Jung *et al.,* 2020) in patients with epilepsy for interpreting the occurrence of atherosclerosis in association with seizure disorders (Talaat *et al.,* 2015; Ramírez-Moreno, 2020) that might change with age (Jung *et al.*,2020; Markozannes *et al.,* 2021). Pathophysiological mechanisms for increased risk for epilepsy associated with vascular risk were suggested as related to atherosclerosis and related complications (Ramírez-Moreno, 2020). Hence, it was planned to study the age-based variations in male patients with epilepsy. However, it was necessary to manage for the influence of wide variation of BMI. Owing to that reason, the present study involved only normal-weight male subjects, and those subjects with overweight or obesity status were not included, since overweight/ obesity status might be involved in causing systemic inflammation.

Some of the investigations in the present study provide evidence for previous studies manifesting the association between inflammation and epilepsy though in different perspectives (Woernle *et al*., 2013; Chen *et al*., 2018; Zhong *et al*., 2019). Research work in epilepsy conducted based on age and sex (Meguid *et al.,* 2018) showing elevated levels of CRP, and other studies showing systemic changes after CRP elevation (Matsuo *et al.,* 2014; Kes *et al.,* 2016) further confirm the present results. Hence, it seems possible that epilepsy disorders manifest a little or more extent of inflammation whereby CRP elevation occurs. In this relatedness, the present study can be explained by the occurrence of focal or systemic inflammation in causing the hyperexcitability leading to epileptogenesis as has been suggested previously (Musto *et al.,* 2016; Paudel *et al.,* 2018; Terrone *et al.,* 2019).

A limitation of the present study was that the age range was quite limited. However, other studies with a wider age range indicated an increase in CRP levels with age, though in younger subjects, but not in older people (Qiu *et al.,* 2016). The age-based elevated levels of CRP might have been due to weakened innate and adaptive immunity

(Gao *et al.*, 2014). The present data show similar suggestions as presented earlier (Wada *et al.*, 2008; Lavallée *et al.*, 2013; Gao *et al.*, 2014; Gong *et al*., 2019). Further studies may confirm the precise role of CRP levels in epilepsy involving ischemic/ inflammatory disorders.

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