**C-Reactive Protein and Stroke: A Review of Literature**

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**Abstract:**

Stroke is a major cause of neurological morbidity and mortality. C-reactive protein (CRP) is a blood marker of inflammation and a hallmark of the acute-phase response. Its elevation bears negative prognostic implications for many conditions and it has also been shown to be a nonspecific predictor of long-term risk of cerebrovascular diseases (CVD). High sensitivity C-reactive protein (hsCRP) has been evaluated as a biomarker in stroke and relevant pathological diseases. While its predictive values in several pathological phenotypes have been reported, controversy exists among different studies. This review summarizes reports of the predictive values of hsCRP for the diagnosis, etiology, prognosis and mortality of stroke diseases.

**Key words:** c-reactive protein, stroke, predictor

**Introduction:**

It is known that inflammation is involved in the pathophysiology of acute ischemic stroke. It has been proven that CRP is useful in predicting a prognosis for stroke patients (Kocaturk 2019). Inflammation has been proposed to contribute to CVD in several ways, which including: (1) the lifelong process of atherogenesis; (2) the acute atherothrombotic event, which causes ischemic necrosis in acute cerebral infarction and the brain damage following ischemic stroke; (3) delayed brain injury after intracerebral hemorrhage; (4) vasospasm after subarachnoid hemorrhage (SAH).

CRP, the classical acute phase protein, is among the most extensively studies systemic maker of inflammation. Previously, CRP has been the focus of intense investigation to identify its complex role in CVD after the introduction of hsCRP assays able to detect low levels of blood CRP. hsCRP has been used as a CVD risk biomarker, as a pathogenetic determinant with a direct causal role in stroke pathogenesis, and as a short- and long-term predictor of stroke outcomes. The objective of this article is to provide an overview of the available evidence on associations of CRP with stroke.

**Structure of CRP:**

CRP is an acute-phase protein featuring a homopentameric structure and Ca-binding specificity for phosphocholine (PCh) (Black S et al, 2004). Expression of CRP is regulated mainly at the transcriptional level with interleukin-6 being the principal inducer of the gene during the acute phase. The crystal structure of CRP has been determined and the topology and chemical composition of its ligand-binding site determined (Thompson et al, 1999). The wide distribution of PCh in polysaccharides of pathogens and in cellular membranes allows CRP to recognize a range of pathogenic targets as well as membranes of damaged and necrotic host cells. CRP bound to a multivalent ligand can efficiently initiate the assembly of a C3 convertase through the classical pathway and thus decorate the surface of the ligand with opsonic complement fragments. However, the protein does not favor the formation of a C5 convertase and therefore, CRP initiated complement activation does not mediate acute inflammatory reactions and membrane damage. CRP also interacts with Fc receptors on phagocytic cells and acts as an opsonin (Oliveira et al, 1979). Other CRP initiated signals through interactions with neutrophil Fc receptors have an overall anti-inflammatory effect. Thus, the main biological function of CRP appears to be host defense against bacterial pathogens and clearance of apoptotic and necrotic cells. Protection from lethal bacterial infection, from complement-induced alveolitis, and from endotoxemia has been confirmed in vivo using transgenic mice. Additional functions, including participation in atherogenesis and pathogenesis of myocardial injury after myocardial infarction have been reported.

**Ligand binding by CRP:**

CRP binds to phosphocholine (PC) and related molecules on microorganisms and plays an important role in host defense. However, a more important role may be the binding of CRP to PC in damaged membranes. CRP increases clearance of apoptotic cells, binds to nuclear antigens and by masking autoantigens from the immune system or enhancing their clearance, CRP may prevent autoimmunity. CRP binds to both the stimulatory receptors, FcgammaRI and FcgammaRIIa, increasing phagocytosis and the release of inflammatory cytokines; and to the inhibitory receptor, FcgammaRIIb, blocking activating signals (Marnell et al, 2005).

**Function of CRP:**

CRP is an ancient highly conserved molecule and a member of the pentraxin family of proteins. CRP is secreted by the liver in response to a variety of inflammatory cytokines. Levels of CRP increase very rapidly in response to trauma, inflammation, and infection and decrease just as rapidly with the resolution of the condition (Volanakis JE, 2001). Thus, the measurement of CRP is widely used to monitor various inflammatory states. CRP binds to damaged tissue, to nuclear antigens and to certain pathogenic organisms in a calcium-dependent manner (Du Clos TW, 2000). The function of CRP is felt to be related to its role in the innate immune system. Similar to immunoglobulin (IgG), it activates complement, binds to Fc receptors and acts as an opsonin for various pathogens. Interaction of CRP with Fc receptors leads to the generation of pro-inflammatory cytokines that enhance the inflammatory response. Unlike IgG, which specifically recognizes distinct antigenic epitopes, CRP recognizes altered self and foreign molecules based on pattern recognition. Thus, CRP is thought to act as a surveillance molecule for altered self and certain pathogens. This recognition provides early defense and leads to a proinflammatory signal and activation of the humoral, adaptive immune system.

**Metabolism of CRP:**

CRP is mainly produced by hepatocytes in liver which affects plasma concentration in a minute. CRP synthesis is under gene transcriptional regulation via pro-inflammatory factors including interleukin (IL)-6, IL-1 and tumor necrosis factor-a (TNF-a). Any form of tissue injury, infection, inflammation and stress are associated with increasing of plasma CRP values (Kushner et al, 2006). CRP is obviously cleared from the circulation and catabolized exclusively by hepatocytes. The plasma half-life of CRP in humans is about 19 hours which is no difference among individuals regardless of health condition and its original concentration (Hutchinson et al, 1994). Therefore, the synthesis rate of CRP decides the plasma CRP concentration. It is very important for any interpretation of the signiﬁcance and utility of CRP values to distinguish between modest increments in the very low normal baseline values of CRP. The massive rises of several orders of magnitude which occur very rapidly following major stimuli, such as sepsis, acute trauma or tissue necrosis. High level of CRP may persist for months or years in individuals with chronic active inﬂammatory and tissue damaging diseases, such as chronic infections, rheumatoid arthritis, Crohn’s disease, lymphoma and many others. Because CRP response can be caused by so many conditions, we cannot interpret CRP values in an individual without obtaining full clinical information on that person. The clinical information include history, physical examination and full results of all available investigations (Pepys and Hirschﬁeld, 2003).

**Concentration of Circulation CRP in healthy normal populations:**

Serving as a primary defense function of the human body, CRP levels are detected within the limits of 6 to 10 mg/L using a technique known as nephelometry. Of all ethnic backgrounds, the Asian population tend to have the healthiest levels of <0.15 mg/L. Compared to those residing in the Western region of the world, a collective report including over 20,000 able-bodied U.S. partakers had the following results; the 10th, 50th, and 90th percentile values for CRP were 0.40, 1.50, and 6.05 mg/L for men and 0.29, 1.52, and 6.61 mg/L for women, respectively. Participants from Japan had the following outcomes; with the 10th, 50th, and 90th percentile values being <0.03, 0.16, and 0.78 mg/L for Japanese men and <0.03, 0.09, and 0.57 mg/L for Japanese women, respectively (Rifai and Ridker, 2003).

Following the trends of most health-related issues, CRP levels are boosted by employing bad habits and curtailed with a healthy diet. In a decade long longitudinal study, over 1,500 apparent healthy participants from both genders (age 70-90 years) from 11 European countries, adhered to the diet along with a healthy lifestyle. Findings showed that they had a mortality rate 50% lower than the control group (Knoops et al, 2004).

In another longitudinal study, pre- and perimenopausal woman between the ages of 42 – 52 years had their CRP measurements conducted. Members of the study had their weight, height, and hip circumferences measured along with their vitals. Again, the Asian population had the lowest levels of CRP while African-Americans led the pool of contributors. African-Americans had a median of 3.2 mg/L, and an interquartile range (IQR) 1.1-7.7. Hispanics followed with 2.3 mg/L, IQR 1.0-5.1, and then Whites with 1.5 mg/L, IQR 0.6-4.1 (Kelley-Hedgepath et al, 2008).

Lastly, a third longitudinal study by the National Center for Health Statistics utilizing over 5,000 US civilians tracked serum concentrations of CRP from 1999 – 2004. In this six-year study, researchers linked high CRP levels to obesity classes. There was a positive association between CRP concentration and each of the BMI levels (p < 0.01). The mean CRP level for the reference group, which consisted of non-smoking, white males with a BMI <25 kg/m2, was 0.05 mg/dl. The most significant increase came with participants with a BMI ≥ 40.0.

**CRP and stroke:**

Stroke has been brought significant health burden for individuals and society. Early identification and intervention can improve the prognosis of this disease. Since 1990, experimental and clinical evidence accumulatively have shown that inflammation plays a key role in atherogenesis (Libby 2002). CRP is among the most studied inflammation biomarkers. CRP is an acute phase reactant protein produced predominantly by hepatocytes under the influence of cytokines i.e. interleukin (IL)-6 and tumor necrosis factor-alpha. It is markedly up regulated in atheromatous plaques where it promotes LDL cholesterol uptake by macrophages, which is a key step in atherogenesis (Torzewsky et al, 2000). There is increasing evidence showing that inflammatory process is being involved in cerebral ischemia. An elevated CRP levels may predict future ischemic stroke (Arvin et al, 1996). In addition, raised CRP levels may reflect the clinical course of the condition extent of brain infarction and an adverse prognosis (Arvin et al, 1996).

In January 2003, the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) announced a statement for health care providers concerning inflammation markers in cardiovascular disease (CVD) and their application to clinical and public health practice (Pearson et al 2003). High CRP level is associated with stroke severity at admission and is an independent predictor of early seven days mortality after ischemic stroke (Dewan and Rana , 2011).  In whites, the risk was elevated for CRP in the range from 3 to 10 mg/L and even higher for CRP >10 mg/L, whereas in blacks, an association was only seen for CRP >10 mg/L. CRP may not be equally useful in stroke risk assessment in blacks and whites (Evans et al, 2019). Recent findings have demonstrated the important contribution of inflammation to the risk of cardiovascular disease (CVD) in individuals with optimally managed low-density lipoprotein cholesterol (LDL-C). In this high-risk population, low hs-CRP (<2 mg/L) appeared to be associated with reduced risk of incident stroke, incident CHD, and CHD death, whereas low LDL-C (<70 mg/dL) was not associated with protective effects (Penson et al, 2018).

**CRP and risk stratification in stroke:**

Typically, traditional methods for measuring serum CRP are available for use in patients with infectious and inflammatory disorders. which have a detection limit that in the range of 3 to 5 mg/L. That standard is above the concentration observed in most apparently healthy individuals. High sensitivity methods for measurement of CRP (hs-CRP) detect concentrations down to 0.3 mg/L. The assays are necessary for cardiovascular risk stratification, which is based upon discrimination of CRP levels extending below 3 mg/L. This test is sensitized to detect CRP levels less 1 mg/dl (10micgm/ml). Some studies summarize quartiles and tertials of CRP values (lowest <0.55, low-moderate 0.56-1.14, moderate-high 1.15-2.10, highest > 2.11) and the associated probability of a cerebrovascular event. The studies were consistent in their finding of a concentration-dependent relationship between the concentration of CRP and the risk of incident stroke. During the follow-up of 4.9±1.4 years, patients with CRP ＜1 mg/L had 32% reduction compared with that of patients with CRP ≥ 1 mg/L. The control of CRP levels appears to be effective for preventing recurrent stroke and TIA in patients with non-cardiogenic ischemic stroke (Kitagawa et al, 2018). CRP level ⩾5mg/l and SNP rs1800947 of the CRP gene were independent risk factors for further adverse CV events among patients with CVD within three years follow-up (Schulz S et al, 2016).

**CRP and the evaluation of long-term risk of stroke:**

Previously, measurement of CRP has been introduced into routine clinical practice. However, it is more important to examine critically the predictive role of CRP in primary and secondary stroke risk. This should clarify other determinants of CRP in plasma, evaluate the cost effectiveness of measuring CRP, and identify the role of CRP in cerebrovascular pathogenetic mechanisms to facilitate the development of potential new pharmacological treatments. Because stroke risk prediction based only on conventional risk factors such as blood pressure (BP) is still not completely reliable, a continued search for predictive markers is of interest. CDC and AHA recommended plasma CRP measurement as an adjunct to use of established risk factors for assessing the risk of coronary heart disease (CHD) in persons with a calculated 10-year CVD risk of 10% to 20% (Pearson et al, 2003). In December 2003, a European study group was formed to review the scientific evidence relating CRP measurement to stroke risk assessment in subjects at risk for cerebrovascular disease and in stroke patients. An evidence-based approach was used to consider the recommendations for applying CRP as a screening tool (Barratt et al, 1999). Several prospective studies have demonstrated that a single, non-fasting measurement of CRP in apparently healthy individuals is a predictor of future fatal and nonfatal cerebrovascular events (Ford et al, 2000; Ridker et al, 2000; Rost et al, 2001).

The relationship between a patient’s baseline concentration of CRP and future cerebrovascular risk has been consistent in different studies and in most cases has proven to be independent of age, smoking, cholesterol concentrations, BP, and diabetes, the major risk factors evaluated in daily clinical practice. These effects are present in women and men, the elderly and middle aged, smokers and nonsmokers, and those with and without diabetes mellitus. The value of CRP for assessing cerebrovascular risk remains significant after adjustment for the risk factors typically used in global risk-assessment programs (Ridker et al, 2001). All analyses from these studies provide information about relative risks, we know little or nothing about predictive values and absolute risk for cerebrovascular disease (Horowitz and Beckwith 2000). Those subjects with evidence of inflammation not only had higher BP at study entry but also were more likely to have a greater BP increase over time than those without increased markers of inflammation (Engstrom et al, 2002).

In secondary prevention, the role of CRP is evolving rapidly. Multiple studies demonstrate that CRP concentrations are predictive of future CVD events in stroke patients and are independent of the predictive value of conventional prognostic markers (Di Napoli et al, 2001; Iyigun and Bakirci, 2002). Importantly, plasma CRP concentrations in ischemic stroke patients predict outcome or new vascular events independently of age, stroke severity, and other prognostic factors. However, appropriate clinical cutoff points for CRP in the setting of acute ischemic stroke have not yet been defined, nor has timing of CRP evaluation in relation to the onset of the qualifying event been determined. Although no large study has prospectively assessed the value of CRP for prognostic short-term and long-term stratification of patients with ischemic stroke, many data suggest that CRP might be of value in this group of patients (Arenillas et al, 2003; Muir et al, 1999).

After investigation of the relationship between CRP and homocysteine on follow-up and subsequent mortality in young ischemic stroke patients in a population-based study. A study found that there is an independent association between CRP and homocysteine levels obtained several years after ischemic stroke in young adults and subsequent mortality, even when adjusting for traditional risk factors. This association seems to continue for at least 12 years after the measurements (Napoli et al, 2006). In a population-based study of stroke with 5 years follow-up, the level CRP was measured in the acute stroke phase. CRP has a significant direct correlation to the severity of stroke. In addition, the level of CRP at admission may have a clinical implication to identify those at a higher risk of death or recurrence (Mobarra et al, 2019).

Previous studies have shown that elevated CRP levels are associated with increased mortality and poor outcome in patients with myocardial infarction. In stroke patients, CRP measured in the acute phase is associated with long-term mortality regardless of age (Idicula et al, 2009). However, CRP measured in the acute phase of stroke may be influenced by several factors, such as stroke severity and infection. It has also been shown that the CRP level changes considerably during the acute phase and that the pattern of change is highly variable between patients (Di Napoli et al, 2001). Therefore, CRP may be of limited value in predicting long-term mortality in the acute phase of stroke

**Conclusion:**

The pathophysiological processes following stroke are quite complex. Understanding of pathophysiology can help improve current clinical conditions of stroke, including diagnosis, assessment, prognosis and therapy. Meanwhile, CRP as a major bio-inflammation marker reflecting relevant events in the ischemic cascade would also be of great use.

Though a number of studies related to CRP and stroke have been reported, there is much difficulty in successfully translating this advancement to remarkable application in clinical practice. Many of them are related to the underlying pathophysiology of ischemic stroke. The pathogenesis of stroke is complex, involving multiple mechanisms, in this way, the detection of stroke by use of CRP may require multiple markers to capture simultaneously all processes underlying the ongoing ischemic event. Clearly there is much work needed before promising CRP can be introduced into the clinical practice.

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