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Review article

High-sensitivity C-reactive protein in stroke patients – The importance in consideration of influence of multiple factors in the predictability for disease severity and death

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ABSTRACT

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 confirmed, 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. The current literature suggests that CRP expression is influenced by multiple factors, such as polymorphisms, the genomic backgrounds and gender. However, few reported studies analyzed data based on all these multiple factors. Future studies should focus on comprehensive analysis based on multiple factors.

1. Introduction

Stroke is a major cerebrovascular disease threatening human health and life with high morbidity, disability and mortality [1]. According to the data from Global Burden of Disease Study [2], worldwide in 2010 there were an estimated 11,569,538 incident ischemic strokes and 5,324,997 events of incident hemorrhagic stroke; furthermore, 2,835,419 individuals died from ischemic stroke and 3,038,763 from hemorrhagic stroke. Stroke is the number cause of the death in several countries such as China [3]. Stroke was defined as a sudden onset of loss of global or focal cerebral function persisting for more than 24 h [4]. Biomarkers that predict the occurrence and outcome from ischemic stroke are critical for prevention and treatment. Serum biomarkers are considered to be the most valuable adjunct to routine clinical examination and imaging data [5]. Inflammation has an important role in the development of atherosclerosis and during the ischemic event. Inflammatory markers such as fibrinogen and hsCRP have been reported as a predictable marker for the stroke severity and outcome [6]. It has been reported that it is possible to use the increase in the concentration of acute phase reactants especially the hsCRP to help predict cerebrovascular mortality [7].

Human CRP (Pentraxin 1, Ptx1) is an acute phase reactant that is rapidly produced by the liver after tissue injury or infection [5,7]. CRP is a sensitive indicator of inflammation [8,9]. Although many inflammatory biomarkers have been reported to be useful in predicting clinical outcome after stroke, hsCRP remains one of the most widely used in clinical practice [8–12]. Increased hsCRP has been associated with the development of atherosclerosis, ischaemic attacks, hemorrhagic stroke, as well as disease outcomes [13–17]. Studies suggest that post-stroke inflammatory responses may exacerbate tissue damage after cerebral infarction and affect clinical outcomes [18,19]. Recent studies have shown that elevated hsCRP values independently predict the risk of future cardiovascular diseases and ischemic cerebrovascular diseases, including transient ischemic attack in the elderly [20–22]. After acute ischemic stroke (AIS), a sustained inflammatory response indicated by increased level of CRP has been reported in about 75% of patients. A strong and persistent inflammatory response is associated with a worse outcome. Moreover, CRP at discharge has been shown to be

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related to a 1-year outcome [23–25]. Recently, a meta-analysis suggested that elevated baseline hsCRP levels are independently associated with excessive ischemic stroke risk.

However, the physiologic role of CRP is not well understood; it potentially has anti-inflammatory properties as well as pro-inflammatory effects [26]. Inflammation may not only be the consequence of brain infarction, it may also contribute to ischemic damage. In addition, the role of inflammatory markers in predicting functional outcome in stroke remains controversial [27]. This review summarizes the data on the predictive value of hsCRP for ischemic stroke, analyzes the potential influence of CRP on functional outcomes, and identifies the critical issues that are important for the future studies.

2. CRP

CRP (protein CRP) is named because of its precipitation reaction with phosphocholine moiety of pneumococcal cell wall C-polysaccharide. According to the information on Ensembl data base (http://useast.ensembl.org/Homo_sapiens/Gene/Summary?db=core;g=ENSG00000132693;r=1:159712289–159714589), the CRP gene is located on human chromosome 1, between 159,712,289 and 159,714,589 bps. It has 7 transcripts, of which 5 encode proteins. Although the detailed functions of these protein variants are not fully known, the protein with 224 aa produced by the CRP-001 transcript is commonly known as the CRP protein. The protein is a member of the pentraxin family of proteins. The pentraxins are an ancient family of proteins with a unique architecture found as far back in evolution as the Horseshoe crab. CRP structure is strong phylogenetic conservation and high resistance to proteolysis [28]. Therefore, it is relative stable and easy to be measured.

Expression of CRP is regulated mainly at the transcriptional level by cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor; among them, interleukin-6 is the primary circulating physiologic mediator [26]. Recent studies have examined the effects of IL-1β, the IL-1 receptor antagonist anakinra and the IL-6 receptor blocker tocilizumab on the regulation of expression of CRP [29]. An estimation suggests that inter-individual variation in blood CRP level is 35–40% heritable [30] and it is affected by gene polymorphisms. The expression of CRP is also influenced by environmental factors such as bacterial infection and injury. Plasma CRP concentrations increase rapidly and dramatically (100-fold or more) in response to tissue injury or inflammation. Therefore, high levels of CRP (10–1000 mg/L), are associated with serious infections or inflammatory diseases such as arthritis. The hsCRP, on the other hand, measures CRP in the low range, from 0.5 to 10 mg/L. At such range, the hsCRP test is used to identify low but persistent levels of inflammation. The hsCRP is more precise than standard CRP when measuring baseline concentrations. Induction of an hsCRP is rapid and its half-life is long enough in the blood for a steady time course. Therefore, plasma hsCRP is very useful for the diagnostic workup of inflammatory and infectious diseases [26].

3. HsCRP level in early diagnosis of stroke

At present, the diagnosis of stroke depends on clinical examination and neuro-imaging techniques [31]. It is critically important to identify effective biomarkers for the early diagnosis of acute stroke and to establish biological procedures for early diagnosis [5]. Early studies of different populations suggested that modest elevation of hsCRP is a predictor of future vascular events in apparently healthy individuals [32,33]. However, there are few data on the value of hsCRP for the early diagnosis of ischemic stroke.

In 2012, Youn et al. reported in the Keran population that higher hsCRP levels were associated with larger infarct volumes in AIS (Table 1) [26]. Their results suggest that elevated hsCRP levels may serve as a helpful serologic marker in the evaluation of the severity of AIS [34]. Kanai et al. investigated the reciprocal association between serum levels of hsCRP (Table 1) and intercellular adhesion molecule-1 (sICAM-1) and the risk of brain infarction in type 2 diabetic patients [18]. Their study suggests that both measurements of hsCRP and sICAM-1 levels are useful as a predictor of future stroke in diabetic subjects [34]. However, these studies are in Asian population. These findings have not been confirmed in the other regions such as US and European countries.

4. HsCRP in the prediction of atherosclerosis—artery stenosis or occlusion

Ischaemic stroke accounts for 70–80% of all cases of stroke [35]. Ischaemic stroke is mainly caused by atherosclerosis and thrombotic obstruction of cerebral blood flow (Table 1) [36,37]. Atherosclerosis, as a complex and systemic disease, may unequally induce intracranial stenosis, which may in turn impose the limitation of particular inflammatory mediator in describing atherosclerosis [38,39]. Middle cerebral artery stenosis is also associated with advanced age, hypertension, diabetes mellitus and hyperlipidaemia. The risk of stroke increases with the prevalence of atherosclerosis. Therefore, identification of biomarkers for atherosclerosis—artery stenosis or occlusion is essential for the early prevention of stroke. Considerable studies have already shown that an elevated serum CRP level reflects an increased tendency for plaque rupture and a high atherosclerotic burden [13,32,33,40–42].

In 2011, Whiteley et al. showed that higher levels of hsCRP, along with IL-6 and fibrinogen measured after stroke onset in 817 patients are significantly associated with increased incidence of occlusive vascular events and vascular death, as well as nonvascular causes of death after stroke [43]. In a prospectively study of intracranial large artery atherosclerosis progression in 25 of 75 patients using transcranial Doppler follow-up during a median follow-up time of 23 months, Arenillas et al. reported that hsCRP and plasminogen activator inhibitor-1 measured 3 months after onset of ischemic stroke are highly predictive of intracranial large artery atherosclerosis progression [44]. Similarly, Yoshida et al. showed that CRP, along with IL-6 and protein-conjugated acrolein (PC-Acro) is the risk factor for carotid atherosclerosis [45]. In a study on the transcription levels of ABCA1, ABCG1 and SR–BI and plasma CRP in Chinese populations with various risk factors for atherosclerosis, Li et al. reported that circulating CRP was increased almost in all the risk populations except in males [46]. Similarly, hsCRP and Lp-PLA2 was found to improve ischemic stroke risk prediction in the Atherosclerosis Risk in Communities study [47].

At the same time, there are also negative reports. In a study of the association between inflammatory biomarkers and progression of intracranial large artery stenosis after ischemic stroke, Shimizu and colleagues reported that the Cox proportional hazard analysis did not show a significant association between hsCRP and intracranial large artery atherosclerosis progression. The authors concluded that, because the effects of inflammatory factors may continuously affect the vessel walls during the post stroke period, the biomarkers may be more predictive in the chronic rather than the acute stage of stroke and may be important for ILA progression [41]. In a study of the influence of polyvascular atherothrombotic disease on stroke patient prognosis, its relation with inflammatory markers and the progression of atherothrombotic disease, Blanco et al. found a non-significant trend to higher hsCRP levels in patients with vascular recurrences [19]. The authors explained that this is possibly because the calculation of the sample size was based on incorrect assumptions regarding IL-6 levels [42].

The above data suggest that the hsCRP is associated with the progression of atherosclerosis and possibly with artery stenosis