BRITISH MEDICAL JOURNAL

British Medical Journal

Volume 2, No.5, September 2022

Internet address: http://ejournals.id/index.php/bmj
E-mail: info@ejournals.id
Published by British Medical Journal
Issued Bimonthly
3 knoll drive. London. N14 5LU United Kingdom
+44 7542 987055

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ROLE OF ADHESION MOLECULES AND INFLAMMATORY BIOMARKERS IN ISCHEMIC STROKE

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Abstract: This article is devoted to a review of the literature, which presents on the role of adhesion molecules and inflammatory biomarkers in ischemic stroke, as well as aspects requiring detailed study on this issue.

Keywords: Ischemic stroke, inflammatory biomarkers, adhesion molecules.

Introduction.

The World Health Organization defined "stroke" as a clinical syndrome characterized by a rapid onset of focal (or global in the case of coma) cerebral deficit lasting more than 24 h or leading to death, due to a vascular ischemic cause [1]. Ischemic stroke (IS) accounts for the majority of strokes and includes cryptogenic, lacunar, and thromboembolic strokes and it occurs usually when the blood supply to an area of the brain is interrupted [2]. Classical risk factors include age, cigarette smoking, diabetes, hypertension, and obesity. Prone-to-embolism diseases, such as cardiac valve disease and atrial fibrillation, increase the risk for IS, with the latter representing the most frequent condition. In IS, inflammation plays a pivotal role exerting both beneficial and detrimental effects. In fact, activation of resident cells, such as microglia, astrocytes, and endothelial cells is neuroprotective and promotes brain regeneration and recovery, whilst the recruitment of immune cells expressing inflammatory mediators and leading to blood-brain barrier (BBB) disruption is responsible for neuronal death, brain edema, and hemorrhagic transformation [3]. The sudden blockage of blood flow to the brain causes tissue hypoxia and triggers an inflammatory cascade leading to impairment of ion homeostasis, neuronal excitotoxicity, intracellular calcium overload, free radical generation, and lipid peroxidation ultimately determining neuronal injury [4].

2. Cellular response to ischemic stroke

Inflammation is characterized by the accumulation of inflammatory cells and mediators in the ischemic brain. After ischemia onset, inflammatory cells such as blood-derived leukocytes and microglia are activated and accumulate within the brain tissue subsequently leading to inflammatory injury.

2.1. Leukocytes

4–6 h hours after ischemia onset, circulating leukocytes adhere to vessel walls, leading to migration and accumulation into ischemic brain tissue with subsequent release of proinflammatory mediators. These mediators lead to secondary injury of potentially salvageable tissue within the penumbra surrounding the infarct core. Neutrophils are generally the first leukocyte subtype recruited to the ischemic brain, and may potentiate injury by directly secreting deleterious substances or other inflammatory mediators [5]. In transient ischemia, several studies have shown that infarct volume is significantly reduced when neutrophil infiltration is inhibited [6,7, 8,9]. Some mediators, while not directly cytotoxic, may be involved in the destruction of necrotic and neighboring viable tissue. Evidence that neutrophils potentiate ischemic injury include numerous studies documenting improved neurological outcome following neutrophil depletion and inhibition of adhesion molecules which facilitate neutrophil entry into injured brain [10, 11]. The roles of lymphocytes are generally intended to play a negative role in ischemic brain pathogenesis even though there is also conflicting data. Following permanent middle cerebral artery occlusion (MCAO) in rats, lymphocytes were

elevated in the ischemic lesion after neutrophils [12, 13]. Preventing lymphocyte trafficking into ischemic brain ameliorated injury, suggesting that like neutrophils, lymphocytes also play a deleterious role [14]. Clinical studies also show that lymphocytes have a strong pro-inflammatory and tissue-damaging properties, and the upregulation of circulating lymphocytes are correlated to an increased risk of stroke recurrence and death [15]. However, in a study of cultured primary neurons, isolated neutrophils, but not lymphocytes potentiated neuronal injury due to excitotoxin exposure [16].

2.2. Microglial Cells and Circulating Monocytes/Macrophages

Soon after IS onset, microglia is activated and enhances circulating monocyte recruitment by releasing pro-inflammatory mediators, such as tumor necrosis factor (TNF)-α, nitric oxide (NO), and superoxide [17]. Among different possible microglia-activating stimuli, released adenosine triphosphate from damaged cells seems to play an important role in animal models [18]. Microglia activation exerts both beneficial and detrimental effects on stroke outcomes. Once activated, in fact, resident macrophages can polarize toward different phenotypes in response to local ischemic *milieu* ranging from classically activated, pro-inflammatory macrophages type 1 (M1) to alternatively activated macrophages type 2 (M2), which are mainly involved in the resolution of inflammation and tissue healing [19].

In contrast to early microglial response, monocyte-derived macrophages from bloodstream reach the damaged site most abundantly 3–7 days after ischemia onset during the chronic phase of IS [20]. Early after brain injury, an increased number of total monocytes in the blood circulation has been described in humans [21, 22].

2.3. Astrocytes.

Aside from traditional inflammatory cells, astrocytes are known to express different kinds of inflammatory mediators [23, 24]. Following ischemia, brain astrocytes are activated resulting in increased glial fibrillary acidic protein (GFAP) expression and a so-called "reactive gliosis," characterized by specific structural and functional changes [25]. Like microglia, astrocyte proliferation follows two routes A1 a A2 reactive astrocytes. A1 reactive astrocytosis leads to the release of inflammatory factors, namely IL-6, tumor necrosis factor alfa (TNF-alfa), IL-1alfa, IL-1B and interferon gamma (IFNy) and free radicals. Post-stroke, due to failure of the Na+K + pump, astrocytes swell, leading to increased intracranial pressure and cerebral hypoperfusion [26,27]. A2 reactive astrocytes upregulate neurotrophic factors, playing an important role in neuroprotection [26,28]. Disconnection of the astrocyte endfeet and endothelial cells is involved in BBB damage and the influx of peripheral inflammatory cells [26]. In animal models, ischemic cerebral insult induce extensive astroglial response in the lesions core from 4 h to 1 day, peaking at day 4 and persisting until 28 days after [26].

3. INFLAMMATORY MEDIATORS

3.1. Cytokines

Cytokines are small proteins that through extracellular signaling regulate different biological functions such as innate and acquired immunity, inflammation, proliferation and repair. Cytokines have both pro- and anti-inflammatory properties and play an important role in the progression of the stroke-associated inflammation. (29).

3.1.1. Interleukin-1

IL-1 is a pro-inflammatory cytokine, which exists in two forms, IL-1α and IL-1β. Both forms signal through the IL-1 receptor type I, which can be competitively blocked by the receptor antagonist (IL-1Ra) [30]. Both IL-1α and IL-1β levels are elevated in the first hours following an IS. IL-1α is mainly secreted by microglia, while IL-1β is released by different compartments of the NVU [31]. It is surprising to note that IL-1 is not directly toxic, but it is able to activate astrocytes and endothelium favoring astrogliosis, release of chemokines, activation of metalloproteinase (MMP)-9, and release of vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 [32,33,34].

3.1.2. Interleukin-4

IL-4 is a cytokine produced mainly by leukocytes. Its signaling contributes to a potent anti-inflammatory response through the inhibition of proinflammatory cytokines and chemokine among other functions [35]. Although it is poorly studied as a stroke biomarker, Kim and colleagues found that acute ischemic stroke patients had higher levels of IL-4 in serum than controls, [36] while similar IL-4 levels were found in ischemic stroke patients with or without neurological worsening In reference to animal models, functional and cognitive improvement was shown following continuous (starting 6 h after ischemia and lasting for one week) IL-4 administration in a tMCAO mouse model, but without differences in infarct volume when compared with the control group. In contrast, others have found that IL-4 administration decreased infarct volume and improved the behavioral performance and neurological recovery 14 days after stroke in a tMCAO mouse model [38].

3.1.3. Interleukin-6

IL-6 is largely thought of as a pro-inflammatory cytokine, but whether it plays a significant role in ischemic stroke is far from clear. IL-6 deficient mice have similar sized infarcts compared to wildtype suggesting that it does not participate in ischemic pathogenesis [39]. However, other studies suggest either a beneficial or detrimental role. Clinical studies in stroke patients showed that serum concentrations of IL-6 had the strongest independent predictive value for in-hospital mortality [40]. In a double blind clinical trial on patients with acute stroke, IL-6 concentration was much lower in rhIL-1ra, a neuroprotective drug, treated patients, who showed a better outcome compared with placebo treated group [41].

3.1.4. Interleukin-10

IL-10, an anti-inflammatory cytokine, acts by inhibiting IL-1 and TNF-α and also by suppressing cytokine receptor expression and receptor activation. It is synthesized in the central nervous system (CNS) and is upregulated in experimental stroke [42]. Both exogenous administration [43]. and gene transfer of IL-10 [44] in cerebral ischemia models appear to have beneficial effects. Patients with acute ischemic stroke have an elevated numbers of peripheral blood mononuclear cells secreting IL-10 [45] and elevated concentrations in cerebrospinal fluid [46]. Furthermore, subjects with low IL-10 levels have an increased risk of stroke [47].

3.1.5. TNF-α

TNF-α is also upregulated in the brain after ischemia with similar expression patterns as IL-1beta. Initial increases are seen 1–3 h after ischemia onset [48], and, like IL-1beta, has a biphasic pattern of expression with a second peak at 24–36 h [49]. TNF-α expression was initially observed in neurons [48], then later in microglia and some astrocytes [50] as well as in the peripheral immune system [51]. TNF-α appears to have pleiotropic functions in the ischemic brain [52]. Inhibition of TNF-α reduces ischemic brain injury [53], while administration of recombinant TNF-α protein after stroke onset worsens ischemic brain damage [54]. However, TNF-α may also protect the brain under certain circumstances. TNF-α appears to be involved in the phenomenon of ischemic tolerance [55], and mice deficient in TNF receptors have larger infarcts [56]. The reasons for this disparity might be due to different pathways through which TNF-α signals.

3.2. ACUTE PHASE BIOMARKERS

3.2.1. C-Reactive Protein (CRP)

CRP is a protein synthesized in the liver in response to IL-6 secretion by macrophages and T-cells [57]. High sensitivity CRP (Hs-CRP) is more sensitive and can more accurately detect low-grade inflammation. It correlates with cardiovascular risk in the general population and is an inflammatory biomarker frequently associated with all stages of IS [58, 59]. CRP has been shown to be associated with an increased risk of all-cause mortality in patients with acute IS, predicts further ischemic events in patients with transient ischemic attack, lacunar stroke or IS in general [58–59]. Nevertheless, an increase of CRP occurs in IS but also in several other inflammatory

conditions, reflecting its poor specificity and sensitivity [60] CRP is probably more informative with respect to acute indolent inflammatory status that very acute changes in stroke

3.2.2. Procalcitonin (PCT)

PCT is a prohormone of calcitonin and is produced by C-cells and the thyroid gland [61]. Overall, there have been fewer studies than those on other biomarkers like CRP, reflecting its less frequent use in current practice. In ICH, serum PCT correlate with outcome, with higher PCR levels at admission being independently associated with unfavorable clinical outcome [62]. Another study combined albumin and PCT to uncover a ratio, where albumin/PCT ratio could be an additional diagnostic predictor for nosocomial infection in patients with ICH [63]. The role of PCT in CVT has not been investigated.

4. CELL ADHESION MOLECULES.

Cell adhesion molecules (CAMs) play a key role in the trafficking and recruitment of leukocytes to activated endothelia in acute ischemic stroke. In fact, after the ischemic event, there is an increase in CAM expression on the cerebral endothelium. During the progression of inflammation, soluble isoforms of CAMs are shed from the cell surface and released into the bloodstream.

4.1. Intracellular cell adhesion molecule – 1 (ICAM-1)

One of the best-known molecules involved in leukocyte adhesion is ICAM-1. After ischemia, proinflammatory cytokines such as TNF-α, IL-1 and interferon (IFN)-γ up-regulate ICAM-1 on both cerebral endothelial cells and neurons, which appears to be an important feature in driving leukocyte infiltration from blood to brain parenchyma [64]. Soluble ICAM-1 is increased in the blood and cerebrospinal fluid of acute ischemic stroke patients and is associated with neurological deterioration and early death after stroke [65]. On the other hand, the absence of differences in soluble ICAM-1 levels between ischemic strokes and healthy controls has also been documented [66]. This paradox, however, can be partially explained by differences in the methodology used to detect ICAM-1 and the influence that some medications can have over the expression of adhesion molecules, such as non-steroid anti-inflammatory drugs [67]. Therefore, the use of circulating ICAM-1 levels as a biomarker of stroke diagnosis and inflammatory progression after ischemic stroke is not fully corroborated. Further research needs to be conducted to determine the ability of plasma ICAM-1 levels to discriminate ischemic stroke from other neurological and inflammatory diseases. Beyond its role as a biomarker, the inhibition of ICAM-1 has been shown to be neuroprotective by reducing neuronal damage in ischemic rats [68]. Studies of ICAM-1 knock-out mice also reported an improvement in blood flow and a reduction in infarct volume after an ischemic challenge [69], suggesting the impairment of leukocyte migration as a possible therapeutic strategy in improving stroke outcome. Furthermore, at the clinical level the Enlimomab Acute Stroke Trial (EAST) tested the efficacy and safety of inhibiting ICAM-1 through the administration of a murine anti-ICAM-1 antibody. Unfortunately, the Enlimomab-treated group of patients reported a significantly higher fatality rate than the placebo group [70], demonstrating the inefficacy of this therapeutic drug in stroke patients. Nevertheless, there is still some controversy in regards to the experimental design of EAST. The choice of the anti-ICAM-1 treatment regimen and the decision to perform a consecutive 5-day administration are suggested not to be optimally extrapolated parameters compared with the settings used in their respective studies performed in animal models of ischemia. For this reason, ICAM-1 is still suggested to be a possible therapeutic target for improving ischemic stroke outcome, as further studies might corroborate its benefits.

4.2. Vascular cell adhesion molecule 1 (VCAM-1).

Vascular cell adhesion molecule 1 (VCAM-1) is also involved in stroke pathophysiology. VCAM-1, also known as CD106, is a cell surface protein expressed in the endothelium that mediates cell-cell recognition and leukocyte adhesion. VCAM-1 also participates in the downstream signal transduction originated after endothelium activation, directing the immune response to ischemia. High levels of soluble VCAM-1 have been detected in circulation after stroke [71]. Many other inflammatory diseases such as cardiopathies and cancer also present increased levels of soluble VCAM-1 in plasma, suggesting VCAM-1 as an indicator of an inflammatory state [72]. The upregulation of VCAM-1 after stroke is well documented in neurons and endothelial cells after ischemia, which is presumably caused by the elevated levels of cytokines after the ischemic event [67]. Ligand binding to VCAM-1 induces several metabolic and structural changes in endothelial cells that facilitate migration of leukocytes into the brain, which include the production of ROS and the subsequent activation of several MMPs [73]. Recently, VCAM-1 has also been found to participate in neuronal apoptosis after intracerebral hemorrhage, due to the pronounced increase of this adhesion molecule around the hematoma [74]. Thus, all these data attest to the involvement of VCAM-1 in the pathological processes following stroke. The major ligand of VCAM-1 is very late antigen-4 (VLA-4). VLA-4 is an integrin that is constitutively expressed in leukocyte plasma membranes. Upon leukocyte activation, VLA-4 undergoes conformational changes to bind VCAM-1, which contributes to leukocyte penetration of the brain tissue. Thus, VCAM-1/VLA-4 interaction has particular relevance in the immune response and leukocyte infiltration into areas of inflammation. Circulating VLA-4 levels have not been reported in stroke patients up to now, although further studies should check whether these proteins can be found in circulation (soluble form) and be used as inflammatory biomarkers.

Conclusion. IS remains a great burden in modern society. Despite great clinical progresses having been made in recent years in order to improve diagnosis and treatment, beneficial long-term interventions, especially with regard to recovery, are still not available. We now know that the abrupt, dramatic inflammatory response immediately following IS can be evaluated as central or peripheral based on the brain or peripheral tissue origin. In recent years, our knowledge about macrophages has grown considerably as we now can consider M1 and M2 macrophage responses in the post-ischemic period. Apart from widely known cytokines, chemokines, DAMPs, and autoantibodies as well as CAMs represent important inflammatory mediators in the ischemic milieu and need to be considered in a prognostic perspective. Further trials are suggested in order to obtain more information on CAMs profile in order to appropriately select therapy according to each patient. Finally, inflammation is also needed for appropriate post-stroke recovery.

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