New prognostic biomarkers in patients with ischemic stroke

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Ischemic stroke leads to disability and mortality and involved great consumption of resources. This review focuses on new prognostic biomarkers of mortality in patients with ischemic stroke in relation to the inflammation, coagulation, and oxidation. Blood concentration of tissue inhibitor of matrix metalloproteinases (TIMP)-1, soluble CD154 (sCD154), and malondialdehyde (MDA) in ischemic stroke patients have been recently found to be associated with mortality. Matrix metalloproteinases (MMPs) are zinc-containing endoproteinases involved in neuroinflammation during cerebral ischemia and TIMP-1 is the inhibitor of some of them. sCD154 is a member of the tumor necrosis factor (TNF) family that is released into circulation from different cells and when binding to their cell surface receptor showed proinflammatory and procoagulant properties. MDA is a low molecular weight aldehyde and appears due to the attacks from free radical to phospholipids of cellular membrane. The determination of circulating levels of those biomarkers could help in the prognostic classification of the patients. In addition, the modulation of those pathways could open new research lines for the treatment of ischemic stroke patients.

Keywords: Ischemic stroke; biomarkers; TIMP-1; sCD154; malondialdehyde


Introduction

Ischemic stroke leads to disability and mortality and involved great consumption of resources [1]. This review focuses on new prognostic biomarkers of mortality in patients with ischemic stroke in relation to the inflammation, coagulation, and oxidation.

Tissue inhibitor of matrix metalloproteinases-1

Matrix metalloproteinases (MMPs) are zinc-containing endoproteinases, which could be classified according to the substrate specificity in gelatinases (MMP-2 and MMP-9), collagenases (MMP-1, MMP-8 and MMP-13), stromelysins (MMP-3, MMP-10, MMP-11), matrilysins (MMP-7), elastases (MMP-12) and membrane-type (MMP-14, MMP-15, MMP-16 and MMP-17). MMPs are involved in the processes of degradation and remodelling of the extracellular matrix (ECM). MMP activity is regulated by tissue inhibitor of matrix metalloproteinases (TIMPs). MMPs are involved in physiological functions such as morphogenesis, tissue remodelling, menstrual cycle, and angiogenesis; and also in different diseases as tumour, arthritis, sepsis, and atherosclerosis [2].

Cerebral ischemia activate an inflammatory response and are released different cytotoxic agents, such as MMPs, which could favorate disruption of the blood–brain barrier (BBB) and cell damage [3].

There have been found higher circulating MMP-9 levels in ischemic stroke patients than in controls [4-8], and also in patients with ischemic stroke and worse functional outcome compared with patients with better outcome [4-12]. Also,
higher circulating levels of MMP-10 in ischemic stroke patients than in controls there have been found [13]. Besides, there have been found higher TIMP-1 concentrations in brain tissue of patients with cerebral infarction in comparison with brain tissue of healthy cerebral areas [14]; higher expression of TIMP-1 in monocytes of ischemic stroke patients with than in healthy controls [15], higher blood TIMP-1 concentrations in patients with ischemic stroke than in healthy subjects [16-19], and an there is association between neurological clinical outcome and plasma TIMP-1 levels at 7 days of clinical ischemic [20].

In a study by our team was found that patients suffering a malignant middle cerebral artery infarction (MMCAl) showed higher serum MMP-9, MMP-10 and TIMP-1 levels than healthy subjects [21]. Another new finding of our study was that non-surviving MMCAl patients showed higher circulating TIMP-1 and MMP-10 concentrations than survivors, and that there is an association between circulating TIMP-1 levels and mortality. We found on the multiple logistic regression analysis that serum concentrations of TIMP-1 higher than 239 ng/mL, controlling for Glasgow Coma Scale (GCS) and age, were associated with mortality at 30 days (Odds Ratio = 5.82; 95% CI = 1.37-24.73; \( p = \) 0.02). We found an area under the curve (AUC) of serum TIMP-1 levels for the prediction of 30-day mortality of 0.81 (95% CI = 0.67-0.91; \( p < 0.001 \)). In addition, the survival analysis showed a higher 30-day mortality in patients with serum TIMP-1 levels higher than 239 ng/mL than in those patients with lower levels (Hazard ratio = 3.6; 95% CI = 1.67-7.82; \( p = 0.004 \)). Besides, another new findings of our study were the association between circulating TIMP-1 and MMP-10 levels (\( p = 0.001 \)), between circulating TIMP-1 and plasminogen activator inhibitor (PAI)-1 levels (\( p < 0.001 \)), and between circulating TIMP-1 and tumor necrosis factor (TNF)-alpha levels (\( p < 0.001 \)).

In other clinical circumstances, such as patients with coronary artery disease [22], different cancer types [23-26], sepsis [27-29] and trauma brain injury [30], also circulating levels of TIMP-1 have been associated with poor prognosis.

I believed that increased serum levels of TIMP-1 levels in ischemic stroke patients compared to healthy subjects, and in non-survivor patients compared to survivor patients may be due to an increase of circulating levels of MMP-9 and MMP-2, in order to maintain the balance between proteases and inhibitors; and that increased serum levels of TIMP-1 in non-survivors patients compared to survivor patients is not the death cause in these patients, rather a mortality biomarker.

The modulation of MMP activity by different agents have showed a beneficial effect in rat with ischemic stroke by the reduction of MMPs expression, leakage of blood brain barrier, volumen infarction, neurological dysfunction and mortality [31-36]. Thus, could be interesting to research on the use of MMP activity modulators for the treatment of patients with severe ischemic stroke.

**Soluble CD154**

CD154 is a protein included on the TNF family, and is expressed by platelets, B cells, T cells, monocytes cells, natural killer cells, mast cells, basophils, endothelial cells, smooth muscle cells, and microglia. CD154 is released into blood circulation as soluble CD154 (sCD154) [37]. When sCD154 binding to their cell surface receptor then exhibit proinflammatory and procoagulant properties, due that triggers the expression of interleukin (IL)-1, IL-6, IL-12, TNF-alpha, interferon-gamma [38], tissue factor [39-42] and binding to the glycoprotein IIb/IIIa platelet receptor [43, 44].

There have been found a higher CD154 expression in platelet of ischemic stroke patients than in controls subjects [45, 46], higher circulating levels of sCD154 in ischemic stroke patients than in controls subjects [47-54], and a higher CD154 expression in platelet of ischemic stroke patients with poor functional outcome compared with patients with better outcome [55, 56].

In a study by our team were found higher serum levels of sCD154 in MMCAl patients than in healthy subjects [57]. In addition, we found an association between circulating levels of sCD154 and severity of stroke assessed by GCS (\( p = 0.04 \)) for the first time. Besides, we found for the first time, higher serum levels of sCD154 in non-surviving patients than in surviving patients, and an association between serum levels of sCD154 and patient mortality. We found on the multiple logistic regression analysis that serum sCD154 levels higher than 1.41 ng/mmL, controlling for GCS and age, were associated with 30-day mortality (Odds Ratio = 10.25; 95% CI = 2.34–44.95; \( p = 0.002 \)). We found that the area under the curve to predict mortality at 30 days for serum sCD154 levels was of 0.80 (95% CI = 0.66–0.90; \( p < 0.001 \)). In survival analysis was found a higher mortality at 30 days in patients with serum sCD154 levels higher than 1.41 ng/mmL than in patients with lower levels (Hazard ratio = 3.4; 95% CI = 1.58–7.39; \( p = 0.006 \)).

In other clinical circumstances, such as patients with acute coronary syndrome [58], sepsis [59, 60], and brain trauma injury [61], also circulating sCD154 levels have been associated with poor prognosis.
Interestingly, a positive association between circulating levels of sCD154 and tissue factor (p < 0.001) and TNF-alpha (p < 0.001) in patients with severe MMCAI patients was reported for the first time in our study. I think that these associations could lead to a higher inflammatory state and a higher prothrombotic state, and could facilitate a higher brain ischemia and a higher death risk for patients with higher circulating sCD154 levels.

The use of statins in patients with coronary artery disease has decreased circulating sCD154 levels [62-64]. Thus, could be interesting to research on the use of agent modulators of sCD154 for the treatment of patients with ischemic stroke.

**Malondialdehyde**

During cerebral ischemia there is an increase in the appearance of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and the alteration in the balance between pro-oxidant and antioxidant states could lead to oxidative cellular damage [65]. Oxidative stress leads to the peroxidation of membrane lipids, and this process generates several end products, such as malondialdehyde (MDA). MDA is a low molecular weight aldehyde and appears due to the attacks from free radical to phospholipids of cellular membrane; and the determination of MDA levels has been used as an effective biomarker of lipid oxidation [66, 67].

Higher circulating levels of MDA in patients with ischemic stroke than in controls have been found [68-80]; and also there has been found an association between circulating levels of MDA and neurological functional outcome in ischemic stroke patients [81-83].

In a study by our team were found higher serum MDA levels (p < 0.001) in patients with MMCAI than in healthy subjects [84]. In addition, we found for the first time, higher serum levels of MDA in non-surviving than in surviving patients, and that there is an association between serum MDA levels and 30-day mortality. We found that the area under the curve to predict mortality at 30 days for serum MDA levels was of 0.77 (95% CI = 0.63-0.88; p < 0.001). In the multiple logistic regression analysis was found an association between MDA levels >2.27 nmol/mL and 30-day mortality (Odds Ratio = 7.23; 95% CI =1.84-28.73; p = 0.005) controlling for GCS and age. We found in the survival analysis that patients with serum MDA higher than 2.27 nmol/mL presented higher mortality at 30 days than patients with lower levels (Hazard ratio = 2.9; 95% CI = 1.31-6.33; p = 0.005).

Also in other clinical circumstances, such as patients with sepsis [85, 86] and brain trauma injury [87] has been found an association between circulating MDA levels and patient mortality.

I think that those higher circulating levels of MDA in patients with MMCAI than in controls and in non-survivors patients than in surviving, represents a higher lipid peroxidation in non-survivors patients.

In several clinical trials, ischemic stroke patients were randomized to the administration of different antioxidant vitamins (B2, B6, B12, C, E) or not [88-90]; and in the treatment patient group were found lower plasma MDA concentration than in the control group. Thus, the use of antioxidant agents in patients with ischemic stroke could have a beneficial effect.

**Conclusions**

Blood levels of some biomarkers (in relation with the inflammation, coagulation, and oxidation such as sCD154, TIMP-1 and MDA) have been recently associated with mortality in patients with ischemic stroke. The determination of blood concentration of those biomarkers could help in the prognostic classification of the patients. In addition, the modulation of those pathways could open new research lines for the treatment of ischemic stroke patients.

**Conflict of interest**

None.

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