SERUM MATRIX METALLOPROTEINASE - 9 AS A PROGNOSTIC FACTOR OF ACUTE ISCHEMIC STROKE: review article

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Article History: Received: 28.04.2023 **Revised:** 30.05.2023 **Accepted:** 07.06.2023

Abstract:

Background: Globally, people are impacted by the heterogeneous and multifactorial condition known as stroke. The breakdown of the blood-brain barrier (BBB), the development of edoema, the activation of proinflammatory cytokines, and the loss of myelin proteins are all pathogenic events connected to ischemic stroke that are mediated by metalloproteinase-9. In acute ischemic stroke patients, the high level of matrix metalloproteinase-9 is closely linked to infarct extension, neurological impairments, and hemorrhagic transformation.
Objective: This scoping review sought to investigate the information currently available from studies that evaluated the predictive function of serum MMP-9 levels in AIS and their relationship to short-term outcomes.
Data sources: By looking up information in the PubMed and Medscape databases of Medline, as well as the predictive value of serum matrix metalloproteinase-9 levels in acute ischemic stroke that are available till 2023.
Study selection: For inclusion, each study underwent an independent evaluation. If they met the requirements listed below, they were considered: Published in peer-reviewed publications, these English-language studies cover the function of serum matrix metalloproteinase-9 level in acute ischemic stroke prognosis.
Data extraction: Studies were disqualified if they didn't meet the criteria for inclusion. A study's ethical permission, eligibility requirements, proper controls, adequate information, and stated assessment measures were all considered in the evaluation of the study's quality. To gather information about the research results we were interested in, data from each eligible study were separately abstracted using a data collecting form.
Conclusion: A possible predictive biomarker for predicting clinical severity as well as the short-term prognosis in ischemic stroke patients is serum MMP-9.

Keywords: ischemic stroke, Matrix metalloproteinase 9, prognosis.

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INTRODUCTION

Globally, people are impacted by the heterogeneous and multifactorial condition known as stroke. It is regarded as the main global cause of death, disability, and mortality **(1).** Stroke can be either ischemic or hemorrhagic. Ischemic strokes account for 85% of all strokes, making them more common than hemorrhagic strokes **(2).**
It is strongly recommended that only recombinant tissue plasminogen activator be used to treat acute ischemic stroke (AIS). However, recombinant tissue plasminogen activator treatment is only appropriate for a particular group of patients. Investigating the aetiology and metabolic alterations that occur inside the infarct area throughout an AIS is therefore urgently needed. These highlight how crucial it is to create blood-born biochemical markers to aid in the identification of AIS **(3)**.
Pathophysiological pathways such as systemic inflammation, atherosclerosis, as well as neurological disorders have all been related to the matrix-degrading enzymes referred to as metalloproteases **(4).**
These proteolytic enzymes, which ordinarily rebuild the extracellular matrix, are members of a family that binds zinc. Matrix Metalloproteinase-9 primarily attacks type IV collagen, laminin, and fibronectin, the primary components of the basal lamina enclosing cerebral blood vessels **(5).**
It contributes to the pathogenic events that take place during an ischemic stroke, including the breakdown of the BBB, the development of edoema, the activation of pro-inflammatory mediators such tumor necrosis factor-α in addition to interleukin-1b, and the degradation of myelin proteins **(6).**
Inhibition of matrix metalloproteinase-9 may have therapeutic benefits because it is intimately linked to infarct extension, neurological impairments, and hemorrhagic transformation in AIS (9). A promising

indicator of an ischemic stroke is matrix metalloproteinase-9 (10).

The aim of this study was to enhance the prognosis of patients with AIS by determining the quantity of serum matrix metalloproteinase-9 within one day of stroke onset as well as following 15 days of follow-up.

MATERIALS AND METHODS

Data Sources: By researching the impact of serum matrix metalloproteinase-9 level in the prognosis of AIS, which is available until 2023, and using the Medline databases (Pub Med and Medscape),.

Study Selection: For inclusion, each study underwent an independent evaluation. If they met the requirements listed below, they were considered: Written in English and published, Discuss the function of serum matrix metalloproteinase-9 level in the development of AIS in publications from peer-reviewed journals.

Data Extraction: Studies were disqualified if they didn't meet the criteria for inclusion. A study's ethical permission, eligibility requirements, proper controls, adequate information, and stated assessment measures were all considered in the evaluation of the study's quality. To gather information about the research results we were interested in, data from each eligible study were separately abstracted using a data collecting form.

REVIEW OF LITERATURE

Stroke:

Cellular death in the brain, spinal cord, or retina resulting from ischemia was suggested as the definition of stroke by the stroke council of the American Heart Association/American Stroke Association according to: pathological, imaging, or additional evidence of spinal cord, cerebral, or retinal focal ischemic injury in a specified vascular distribution; along with clinical evidence of spinal cord, cerebral, as well as retinal focal ischemic injury according to symptoms continuing over 24 hours or until death **(11)**.

♦ Pathophysiology of acute ischemic stroke:

Pathophysiology of ischemic stroke has two stages **(12)**:

1. At a CBF of roughly 142 ml/100g/min, the brain tissue is functionally affected but structurally intact, a condition known as the ischemic penumbra, in which brain damage is still reversible, the electroencephalogram turns isoelectric, and evoked reactions become aberrant.

2. Brain damage turns into permanent when CBF drops below 6 ml/100 g/min, a condition referred to as cerebral infarction or ischemic core.

Stroke is a complex pathophysiological process that involves energy depletion, a disturbance in ion homeostasis, acidity, intracellular calcium overloading, neuronal excitotoxicity, free radical-mediated lipid oxidation, and the breakdown of the BBB (BBB inflammatory cell infiltration along with glial cell activation). These processes eventually result in the death or necrosis of apoptotic neurons **(13).**

♦ Risk factors:

An individual's risk of having an ischemic stroke is increased by a trait as compared to an individual who does not have that characteristic (14). Romero (15) has a thorough grasp of the risk factors for stroke, and clinical trials have identified successful approaches to reduce the incidence of stroke by changing risk variables. The risk factors are separated into standard and unique categories as well as changeable and non-modifiable categories.

Goldstein et al. (16) classified risk variables according to the quality of the evidence and the probability that they might be changed (non-modifiable, modifiable, as well as potentially modifiable) (well documented, or relatively well documented). Non-modifiable risk factors (those which place an individual at a higher risk of stroke and who might gain benefit from intensive prevention or management of modifiable ones) include age, sex, underweight at birth, ethnic origin, and genetic characteristics. High blood pressure, cigarette smoking, diabetes mellitus, atrial fibrillation as well as further cardiac diseases, dyslipidemia, stenosis of the carotid artery, sickle cell disease, postmenopausal hormonal therapy, poor nutrition, immobility, obesity in addition to body fat spreading are well-documented and modifiable risk factors (those that have supportive evidence from both epidemiological studies and randomized controlled trials showing that they reduce risk). The metabolic syndrome, drug and alcohol addiction, oral contraception, sleep apnea,, hyperhomocysteinemia, increased lipoprotein(a), higher lipoprotein-associated phospholipase, excessive coagulation, inflammation, as well as migraine headaches constitute a few of the less well-documented or just potentially modifiable risk factors ((those lack strong epidemiological data or evidence from randomized trials showing a decrease in stroke risk with modification).

Hankey (14) has also proposed possible additional risk factors for AIS, but as of right now, there is no concrete proof that lowering experience to any of these lowers the risk of stroke. They include:

(1) **Genetic factors/genotypes:** Further forms of genetic markers include the angiotensin-converting enzyme genotype, the factor V leiden mutation, the prothrombin G20210A mutation, the MTHFR mutation, the Human Platelet Antigen Type 1 genotype, factor XIII, apo E, the plasminogen activator inhibitor-1 4G/5G genotype, phosphodiesterase 4D, as well as 5-lipoxygenase-activating protein.

(2) **Inflammatory markers:** Monocyte and leucocyte counts, Soluble CD40 ligand, High-sensitivity C-reactive protein (hs-CRP). Interleukins (IL-6, IL-18), Vascular as well as cellular adhesion proteins, Myeloperoxidase, along with Matrix metalloproteinase-9.
(3) **Infectious agents:** Cytomegalovirus, Herpes simplex virus, Chlamydia pneumonia, Helicobacter pylori, Legionella sp, in addition to Periodontal disease.
(4) **Lipid-related factors:** Low-density lipoprotein (LDL), residual lipoprotein, high-density lipoprotein (HDL) subtypes, lipoprotein-associated phospholipase A2, as well as adiponectin.
(5) **Oxidative stress:** Oxidized LDL.
(6) **Biomarkers of hemostasis/thrombosis/impaired fibrinolysis:** Plasma fibrinogen, plasma protein Z, Anti-von Willebrand factor, Tissue plasminogen activator, plasminogen activator inhibitor-1, Antiphospholipid antibodies, prothrombin fragments 1 and 2, fibrinopeptide A, fibrinogen, factor V, factor VII, as well as factor VIII.
(7) **Platelet-related factors:** Aggregation of platelets, platelet activity, along with the volume and size of individual platelets.
(8) **Functional markers:** Pathological changes in the endothelium, Pulse pressure, arterial stiffness, and arterial compliance Ankle-Brachial Index of Systolic Blood Pressure, Neurohormone called B-type natriuretic peptide, Inadequate Albumin Excretion as well as Cystatin C.
(9) **Other factors:** Homocysteine, Metabolic syndrome, Insulin resistance, and patent foramen ovale (PFO).

Matrix metalloproteinase – 9:

Gelatinase B, also known as Matrix Metalloproteinase 9 (EC 3.4.24.35, 92-kDa type IV collagenase, macrophage gelatinase, and 95-kDa type IV collagenase/gelatinase) is a type of proteinase that breaks down collagen. A class of enzymes known as matrixins, which are members of the zinc-metalloproteinases family, are included in the breakdown of the extracellular matrix. MMP 9 is a type IV collagen metalloproteinase. Gelatin types I and V as well as collagen types IV and V are cleaved by this enzyme.**(17).**

♦ Clinical significance:

Numerous pathogenic processes, including as cancer, placental malaria, immunologic and cardiovascular disorders, have been linked to MMP9. **(17)**.

♦ The function of MMP-9 in pathophysiology of ischemic stroke:

The most extensively researched matrix metalloproteinase in stroke is MMP-9. Laminin, collagen, and fibronectin are just a few of the extracellular matrix (ECM) components that it is liable of destroying. This demonstrates its function in disrupting the BBB, mainly the ECM, after a stroke **(18).**

MMP-9 has been linked to hemorrhagic transformation (HT) during tissue plasminogen activator (tPA) therapy, as well as the aetiology of BBB collapse and consequent vasogenic edoema development after stroke **(19).**

Pro/active MMP-9 production has been reported to increase within hours to days following a stroke, leading to increased levels of MMP-9 in both peripheral as well as central cells, including neurons, glia, endothelial cells, in addition to neutrophils. Higher concentrations of circulating inflammatory cytokines, activated astrocytes and microglia, and enhanced thrombolysis have all been linked to changes in MMP-9 **(19).**

Relationship between MMP-9 and short-term outcome of acute ischemic stroke:

When neutrophils release MMP-9 into the brain tissue, they also release other harmful substances including ROS. This causes resident brain cells to release MMP-9 as well, which contributes to the pathways of cell injury and cell death. Following a stroke, neutrophil-derived MMP-9 actively degrades BBB components, leading to cerebral edoema as well as hemorrhagic transformation, which aggravate stroke severity, induce infarct extension, and increase the risk of mortality as well as disability **(20).**

MMP-9 levels have been discovered to be higher in clinical stroke patients who had ischemic strokes. One of the main genes that are elevated in response to a stroke is MMP-9, according to gene expression analyses of peripheral blood from stroke patients. Additionally, it has been confirmed that MMP-9 is higher in the blood of patients who have had strokes and is associated with a worsening prognosis **(21).**

Patients who reached the hospital within 12 hours of their stroke onset, this increase in MMP-9 was found to be a sign of stroke. MMP-9 levels were also suggested as a indicator that could expect the likelihood of stroke **(22).**

At 24 hours post-stroke, MMP-9 expression was found to correlate with the National Institute of Health Stroke Scale (NIHSS), and at 48 hours post-stroke, it connected with stroke severity as well as poor outcome as measured by the NIHSS. The MMP-9 levels also had a positive correlate with the NIHSS score while a negative correlation with the Barthel Index, which measures ADL activities **(23).**

Regarding the long-term results, MMP-9 was linked to a bad neurological result within 3 months after a stroke, and high levels of MMP-9 were linked to a worse Rankin outcome at this time. Increased MMP-9 levels and this poor result were subsequently linked to larger infarcts and more severe strokes (24). According to Sotgiu et al. (25) both MMP-2 and MMP-9 levels were linked with the severity of the stroke and the size of the infarct.

CONCLUSION

This review demonstrated the importance of MMP-9 as an independent short- and long-term outcome predictor of AIS and as a reliable biomarker of prognosis.

To lessen the burden of negative outcomes, more study is needed, and studies of MMP-9's time-dependent influence on the prognosis following stroke are advised.

Conflicts of Interest/Financial Disclosures: Nothing to declare.

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