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A STUDY ON ROLE OF CYTOKINES IN PREDICTING THE OUTCOME OF ACUTE ISCHEMIC STROKE: A SYSTEMATIC REVIEW

Neurology

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KEYWORDS

INTRODUCTION:

Cytokines are soluble glycoproteins released from inflammatory cells like T helper cells and macrophages in response to stress and diseases. Cytokines include chemokines, monokines, lymphokines, and interleukin. Chemokines are cytokines with chemotactic activities. Monokines and lymphokines are made by monocytes and lymphocytes. Cytokines are made from one leukocytes and act on other leukocytes. [1]

Interleukin and chemokines play a major role in inflammatory changes.

According to World Health Organization, stroke is a clinical syndrome consisting of rapidly developing clinical signs of focal disturbance of cerebral function lasting for more than 24 hours or leading to death with no apparent causes other than a vascular origin [15].

In stroke, occlusion of cerebral artery by a thrombus or embolus causes deprivation of oxygen, glucose, and lipids. Oxygen is necessary for the neurons to survive. Thus, decreased oxygen causes death of neurons leading necrosis of brain tissue. Necrotic brain tissue activates inflammatory mediators in necrotic tissue causing breakdown of blood brain barrier which further promotes transport of inflammatory cells like neutrophils and T cells, and mediators to the site of injury [7]. They release cytokines, that aggravate cerebral infarction leading to destruction of cerebral tissue [3].

Microglial cells, astrocytes, endothelial cells, and neurons in brain secretes both pro-inflammatory and anti-inflammatory cytokines. An increase in pro-inflammatory cytokines and decrease in anti-inflammatory cytokines are correlated with larger infarct size in animal models and thus worst clinical outcome [8].

Cerebral ischemia induces inflammatory response causing activation of cytokines, chemokines, endothelial leukocyte adhesion molecules and proteolytic enzymes [6]. Many interleukins like Tumor Necrosis a (TNF - a), Interleukin 1 (IL-1), Interleukin 6 (IL-6), Interleukin 10 (IL-10), Interleukin 4, Transforming growth factor b (TGF - b) and two main chemokines axis are involved in inflammatory process associated with stroke.

Tumor Necrosis Factor a is involved in inflammatory reaction after stroke. It is increased in neurons during first hours after insult and later in glia and blood borne immune cells. In these cells, there is increased expression of converting enzyme, TACE/ADAM17. It undergoes proteolytic cleavage and produces TNF-a. TNF-a activates it receptors TNFR1 and TNFR2 which has neurotoxic repercussion leading to cell necrosis, activation of caspases and other apoptotic factors. It also activates neuroprotective pathway in stroke. Thus the affect of TNF-a in stroke is controversial. [2]

Interleukin 1 is also involved in ischemic stroke. Precursors of interleukin undergo proteolytic cleavage by multiprotein complexes producing two active forms of interleukin 1 namely interleukin 1a and interleukin 1b. Interleukin 1a is mainly produced in microglia and interleukin 1b is produced in microglia and astrocytes due to ischemia in stroke.

Interleukin 1 binds to its IL – 1 receptor 1 activates endothelial cells which produce more cytokines or chemokines and MMP 9 (Matrix Metalloproteinase 9) leading to blood brain barrier disruption and immune cell infiltration. Interleukin 1 also produces gliosis in ischemic stroke.[2]

Interleukin 6 is released from macrophages and components of neurovascular unit. Similar to IL 1, it also activates endothelial cells producing more and more cytokines and chemokines causing blood brain barrier damage and gliosis. It also has neuroprotective role by stimulating blood brain barrier recovery, angiogenesis, and neurogenesis. Few studies also showed that increased cytokines like IL 6 is associated with stroke risk. Thus, it's role is controversial [10].

Interleukin 10 is produced by T regulatory cells, lymphocytes, monocytes or macrophages and microglial cells in stroke. It has anti-inflammatory effect by suppressing the production of proinflammatory cytokines and protects neuronal cells.

Transforming growth factor b is another anti-inflammatory cytokine similar to IL 10 and inhibits the production of MCP -1 (Monocyte Chemoattractant Protein-1) and Macrophage Inflammatory Protein 1 alpha. It induces gliosis.

Interleukin 4 is also an anti-inflammatory cytokine which is produced by microglia or macrophages, and decreased astroglia activation. It promotes microglial resting phenotype and M2 activation of monocyte / macrophage and thus helps in resolution of inflammation in stroke.

Along with the above-mentioned interleukins, chemokines which help in leukocyte migration are also involved in inflammatory changes after stroke. Two main chemokines axis like CXCL8 (IL-8)/CXCR2 and the CCL2/CCR2 axis are involved in stroke.

The present study aims to study the role of various cytokines in acute ischemic stroke through a systematic review.

Methodology:

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines was adopted throughout this review article to provide a comprehensive framework of a systematic review.
Eligibility Criteria:

- All original research articles on role of cytokines in predicting the prognosis of acute ischemic stroke
- Articles in English language only.
- Articles published in scholarly peer reviewed journals from 2000 to 2023

Information Sources:

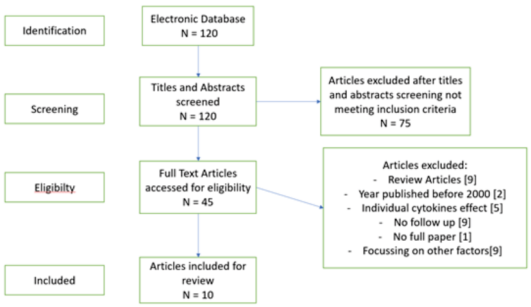
Studies were identified by searching relevant papers in Pubmed Central and Google Scholar.

Search:

The articles in the database are searched using the following keywords: “Cytokines + acute ischemic stroke”, or “cytokines + stroke”

Study selection and Data Collection Process:

Each article and abstract were screened to meet the eligibility criteria. The full text articles were further accessed for eligibility. Data from the studies were recorded and analysed.



Review Of Literature:

Li et al. screened 35 cytokines, chemokines and growth factors in sera of 75 acute ischemic stroke patients and healthy control subjects and found out that IL-1RA, IL-1β, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-13, IL-15, EGF (Epidermal growth factor), G-CSF (Granulocyte-Colony Stimulating Factor), GM-CSF and Fractalkine levels were significantly decreased in severe stroke patient. And level of IL-1β, IL-4, IL-5, IL-7, IL-9, IL-10, IL-15, G-CSF and GM-CSF were significantly reduced in acute ischemic stroke and associated with poor outcome. Among above, IL -6 was significantly higher in poor outcome group. Only IL -9 was decreased in large infarct volume group [3].

Amit R. Nayak et al. estimated 12 inflammatory cytokines in serial blood samples collected at admission, 24 hr, 48 hr, 72 hr, 144 hr and at discharge in acute ischemic stroke patients. IL 10 was found to be decreased after stroke and increased at seventh day after stroke. It was associated with neurological deficit and stroke outcome. IL 6 and TNF alpha were increased within 24 hrs after stroke. Among all the above, IL 2, 10, TNF alpha could be used for the follow up of stroke patient [4].

Vanja Basic Kes et al. studied on concentration of IL 6, TNF alpha and IL 10 in acute ischemic stroke and found that increase in IL 6 was associated with severe stroke and worst outcome. Increased in IL 10 was associated in better outcome. No association was found in TNF alpha [5].

Nicolas Vila et al. assessed the implication of IL 10, IL 4 in deteriorating ischemic stroke. Decreased IL 10 is significantly associated with neurological worsening. No association was found with IL 4 [6].

M Sahan et al. assessed the variations in levels of C reactive protein, white blood cells, fibrinogen, thrombocyte, IL 6, IL 8, IL 10 and TNF alpha in acute ischemic stroke and its association with stroke volume. No significant correlations were found between stroke volume and levels of cytokines (IL 6, IL 8, IL 10, TNF alpha) and C reactive protein. Glasgow Coma Scale (GCS) and NIHSS scores correlated with stroke volume [8].

Hedley C A Emsley et al., serially measured the production of cytokines within 12 hrs of acute ischemic stroke and followed the patients up to 1 year. Peak soluble TNF receptor type 1 correlated in the first week with infarct volume. Minimum Lipopolysaccharide induced cytokine production strongly correlated with mRS (modified Rankin Score). IL-1β, soluble IL-1 receptor type II, tumour necrosis factor (TNF)-α, TNF-RII, IL-10 and leptin concentrations did not significantly differ from controls [9].

Increased levels of proinflammatory cytokines are associated with greater extent of cerebral infarct and poorer clinical outcome in acute ischemic stroke [6].

Hanne Christensen et al. measured the plasma levels of IL 1 beta, TNF alpha, Interleukin 1 receptor antagonist, IL 6, IL 10, soluble TNF R1 and soluble TNF R2 were measured by ELISA (Enzyme Linked Immunosorbant Assay). IL 10 was significantly associated with stroke severity. C reactive protein and white blood cell count were significantly associated with cytokine response [11].

Marios K Georgakis et al., predicted that genetic predisposition to higher MCP 1 levels was associated with higher risk of any stroke, ischemic stroke, large artery stroke and cardioembolic stroke [12].

According to Jun Oto et al., No significant differences in cytokines or catecholamine concentrations was found between patients with poor and good outcomes. There was no association between clinical outcome and cytokine and catecholamine concentrations. IL 6 and IL 10 were higher in patients with poor outcome [13].

Heidi Ormstad et al., IL – 8 was significantly correlated with age in patient group. Infarct volume was significantly positively correlated with CRP level [14].

Article	Year	Cytokines measured	Significance
Nicola´s Vila et al [16]	2000	IL – 6, TNF alpha in plasma and CSF samples	IL 6 was correlated with infarct volume and clinical worsening. TNF alpha was higher in worse outcome
Nicolás Vila et al [6]	2002	IL 10, IL 4	Lower IL 10 levels (< 6 pg/ml) were associated with clinical worsening No significant association of IL 4 were seen with stroke.
Christensen H [11]	2002	IL-1 beta, TNF-alpha, interleukin-1 receptor antagonist (IL-1RA), IL-6, IL-10) soluble tumor necrosis factor receptor 1 (sTNF-R1), and soluble tumor necrosis factor receptor 2 (sTNF-R2)	No significant association
Emsley HC et al [7]	2007	IL 1 receptor antagonist, IL 1 beta, soluble IL 1 receptor type II, TNF alpha, TNF R II, IL 10, leptin, IL 6	TNF receptor type I correlated with infarct volume
Basic Kes V [5]	2008	IL-6, TNF-α and IL-10	Increased IL 6 and reduced IL 10 were association with neurological deficit and poor stroke outcome.
Oto J [13]	2008	IL-1β, IL-6, IL-1 β 0, and TNF-α	No significant association between ncytokine and catecholamine concentrations and clinical outcome. IL-6 and IL-10 were associated with poor outcome.
Ormstad H [14]	2010	Bio-Plex ProTM Human Cytokine Group I; IL-1 β, IL-1ra, IL-2, IL-4, IL-6, IL-8, IL-9, IL-10, IL-12, TNF- α, and interferon- ۲ (IFN-c); Bio-Plex ProTM Human Cytokine Group II; and GRO- α (CXCL1) and IL-18 (Bio-Rad).	IL-1ra, IL-6, IL-8, IL-9, IL-10, IL-12, IL-18, GRO-۵ were significantly higher in acute ischemic stroke IL 8 level was correlated with age of the patient significantly. None of the cytokines were correlated with stroke lateralization. C Reative Protein was correlated with infarct volume. GRO ۵ was specific for stroke.
Nayak AR [4]	2012	IL- 1A, IL-1B, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17A, interferon (INF)y, TNF-α and granulocyte-macrophage colony stimulating. factor (GM-CSF)	IL-10, IL-2 and TNF-a was useful in prognosis of stroke

Sahan M et al [8]	2013	C Reactive Protein, TNF alpha, IL 6, IL 8, IL 10, Fibrinogen, leukocyte	Levels of C Reactive Protein was correlated with prognosis of acute ischemic stroke
Li X [3]	2018	IL-1RA, IL-1β, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-13, IL-15, EGF, G-CSF, Flt-3L, GM-CSF and Fractalkine levels	Reduced levels of IL-1β, IL-4, IL-5, IL-7, IL-9, IL-10, IL-15, G-CSF and GM-CSF were significantly associated with poor outcome

DISCUSSION:

Stroke is one of the most common neurological diseases associated with increased morbidity and mortality. Due to the individual variability of outcome of stroke, there is a need for a biomarker for assessment of prognosis of acute ischemic stroke. This would alert the physician to take further steps to manage the patient.

Cytokines are one of the important inflammatory mediators involved in pathogenesis of acute ischemic stroke. Various prospective observational studies are done to assess the role of cytokines in prognosis of acute ischemic stroke.

Cytokines are a family of soluble glycoprotein which includes various biomolecules.

According to Nicolás Vila et al [16], IL-6 is correlated with infarct volume. According to Basic Kes V [5] and Oto J [13], increased levels of IL-6 is associated with poor outcome, functional deficit and severe stroke.

Nicola´s Vila et al [16] concluded that higher levels of TNF alpha are seen patients with worse outcome. But Majority of above studies concluded that TNF alpha has no correlation with outcome of stroke and thus could not be used as a marker for acute ischemic stroke [4, 5,8, 11]. According to Emsley HC et al [7], TNF receptor type I correlated with infarct volume in acute ischemic stroke.

IL-10 is an anti-inflammatory cytokine which also showed controversial findings. Most of the articles postulated that increased IL-10 is associated with good clinical outcome [4,5,6,11,13]. No significant association is found between IL 10 and outcome of stroke by Sahan M et al [8] and Emsley HC et al [7].

Li X [3] concluded that reduced levels of IL-1β, IL-4, IL-5, IL-7, IL-9, IL-10, IL-15, G-CSF and GM-CSF were significantly associated with poor outcome. But many studies are not done to find the further association of many cytokines.

Thus IL-6 and IL-10 are the two main important cytokines which can be used in assessing the prognosis of acute ischemic stroke.

There is a need to further study the mechanism of action and importance of all cytokines in assessing the prognosis of acute ischemic stroke. Further research is required before concluding the role of cytokines in prognosis of acute ischemic stroke.

CONCLUSION:

There is a scope of using cytokines as a biomarker for predicting the prognosis in acute ischemic stroke. IL-6 could be used in assessing the prognosis of acute ischemic stroke. Though there are few controversies in IL-10, it could also be considered as a biomarker for predicting prognosis. TNF-a could not be used to predict outcome of stroke.

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