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Non Hemorrhagic Stroke (SNH) and Interleukin-6 (Il6): A Literature Review

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Abstract:- The pathophysiology of stroke is a complicated process, and it is thought that neuronal damage is caused by oxidative stress and inflammatory responses. Acute ischemic stroke (AIS)'s pathophysiology relies heavily on the inflammatory response. Raised degrees of fiery markers like C-receptive protein (CRP) and interleukin-6 are related with unfortunate visualization in ischemic stroke. Prostaglandin E2, which stimulates the hypothalamus and raises body temperature, can be released into the brain by interleukin-6. IL-6 articulation in intense stroke still up in the air by infarct size yet additionally under hereditary control. The instrument of IL-6's impact on post-stroke discernment stays unexplained. After a stroke, the chronic inflammatory response may start neurotoxic pathways that cause progressive degeneration. Chemokines, activation of microglia and astrocytes, and neuroinflammation-mediated disorders may also be exacerbated by damaged neurons.

Keywords:- *Stroke, Interleukin-6, Prognosis.*

I. INTRODUCTION

After cancer and myocardial infarction, stroke is the leading cause of disability worldwide and the third leading cause of death. As per information from the World Wellbeing Association (WHO) in 2011 as numerous as 20.5 million individuals on the planet experienced stroke and it is assessed that 85% of them were non-hemorrhagic strokes.[1] In developing countries, the number of stroke patients is quite high and reaches two-thirds of the total stroke patients worldwide. Additionally, developing nations account for 85.5% of stroke deaths worldwide.. In Indonesia, stroke is one of the main non-communicable diseases causing death besides hypertension, ischemic heart disease and other heart diseases. According to the results of Basic Health Research (RISKESDAS) in2007, stroke frequency was 8.3 per 1000 people, with non-hemorrhagic stroke accounting for 60.7% of cases. Up to 28.5% of patients passed away, with the remaining patients were completely or partially paralyzed. Only 15% of people with disabilities or strokes can fully recover.[2]

Ischemic stroke, also known as a non-hemorrhagic stroke, is the third most common cause of death and the leading cause of disability among people over 65. The World Wellbeing Association gauges that one out of six individuals on the planet will experience a stroke in the course of their life. STROKE affects about 0.2 percent of the general population annually. Ischemic stroke is the most regular kind of stroke influencing roughly 85-90% of patients, generally normally brought about via cardiogenic embolism, cerebral microcirculation problems (cerebral microangiopathy), atherosclerosis of extra-and intracranial veins, and thickening problems.[3]

Although the pathogenesis of stroke is complicated, oxidative stress and inflammatory responses are considered to be important processes that lead to brain damage. Reactive oxygen species (ROS) are released by the brain and immune system during ischemia and hypoxia. These ROS excite endothelial cells and result in oxidative stress. In addition to causing primary vascular damage during an ischemic stroke, ROS activity also sets off the development of an inflammatory response linked to an acute immunological response. Activated glia cells (microglia, astrocytes), blood cells (leukocytes), and endothelial cells produce various biochemical mediators and inflammatory indicators, such as proinflammatory enzymes, chemokines, and cytokines.[4]

Numerous factors also contribute to the development of inflammation in stroke patients, with hereditary genes responsible for inflammatory reactions playing a significant role. Furthermore, research has demonstrated that a wide range of genes may influence the genesis of a stroke, the extent of the ischemic region, and ultimately the patient's prognosis. Consequently, the activation of chronic inflammation is a factor that can modify the trajectory of the acute phase of stroke and have a major impact on the development and impact of stroke risk factors.[4]

Potential targets for future stroke therapy include the inflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF). All three cytokines have the ability to control the extent of ischemic damage in focal cerebral ischemia, an experimental form of stroke, and following an ischemic stroke in people, their levels rise in the blood and cerebrospinal fluid (CSF). Evidence suggests that resident microglia, intrathecal macrophages, and invading, monocyte-derived macrophages release TNF and IL-1 in the brain of stroke-affected rats, whereas neurons also produce IL-6. Despite the fact that TNF, IL-1, and IL-6 are likewise the best examined cytokines in CSF and blood in stroke patients, we actually have close to zero familiarity with their accessibility and component of activity in the human cerebrum in the

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beginning stage, up to 4 to 6 hours, after trial stroke acceptance, relating to the remedial window in human stroke.[5]

The discovery that TNF, IL-1, and IL-6 levels in the brain increase several times (by as much as 40–60 times) in the first 24 hours following an experimental stroke has supported the theory that these cytokines' effects on the evolution of infarcts are critically dependent on the cytokine levels that are multiplied in the ischemic region. If this doubled increase in cytokine levels were to determine infarct evolution, however, as will be discussed in this review, the time profile for infarct evolution does not correspond to an increase in cytokine messenger RNA (mRNA) and protein production. On account of long-lasting (ischemic) stroke, the infarct nearly arrives at its last volume a few hours before cytokine creation arrives at its greatest.

II. DISCUSSION

A. Non-Hemorrhagic Stroke

➢ *Definition and Classification*

The 1980 World Health Organization (WHO) definition of a "stroke" as "rapidly developing clinical signs of focal (or global) impairment of brain function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin" has largely shaped the meaning of the term in both scientific and lay literature for decades. Because its purpose is to maximize the identification of all deficits caused by cerebral ischemia (decreased blood supply) or hemorrhage, this definition only describes a clinical syndrome and does not include details about vascular mechanisms. These two hidden conditions produce a comparable clinical picture and require prompt clinical consideration. Of note, at first, "worldwide" debilitation of mind capability simply alluded to patients with subarachnoid discharge and without "central" neurological deficiencies and was many times disregarded by and by. But as research advances, characteristics that point to a global cerebral impairment (such loss of consciousness or impairment) can still occur from a variety of other causes, including with subarachnoid hemorrhage, even though they are not usually linked to focal intrinsic cerebrovascular ischemia.[7]

The 1975 National Institutes of Health (NIH) definition of a stroke is "a transient, focal episode of cerebral dysfunction (including retinal) of vascular origin, of rapid onset that usually lasts 2-15 minutes but sometimes up to one day (24 hours)" with "resolution is rapid and leaves no permanent [clinical] neurologic deficit." Stroke has been distinguished from TIA (transient ischemic attack). Recognizing a spectrum in the duration of clinical features associated with untreated cerebrovascular disorders is the basis for this definition. The majority of deficits that disappear on their own after 24 hours do so within the first few minutes or hours. Utilizing a normalized time highlight recognize present moment from long haul deficiencies gives a "typical" reason for "pooling" data on a huge populace with clinical shortfalls that resolve quickly without perceptible residuals, whether hyperacute treatment is utilized. The 24-hour time point has several advantages, which will be covered later: it is comparatively simple to measure, has been the industry standard up to this point, and can be a crucial indicator of the effectiveness of hyperacute treatment or preventative measures.[7]

Hemorrhagic stroke is caused by a blood vessel rupturing and causing blood to leak into the cerebral cavity, whereas ischemic stroke is caused by a blood vessel obstruction that limits the blood flow to the brain. Hemorrhagic stroke can be categorized as either subarachnoid or intracerebral hemorrhage, depending on where the blood leak occurred. 60–80% of strokes are ischemic in nature.[9]

The Oxfordshire Community Stroke Project (OCSP), sometimes referred to as the Oxfordshire or Bamford classification, categorizes stroke based only on clinical abnormalities that can be resolved in the emergency department (ED). Only clinical findings are used for this classification. It can be treated in the emergency room and classifies strokes according to the brain region affected.[9]

- *Total Anterior Circulation Syndrome (TACS) Includes all:*

✓ Unilateral motor, sensory deficits, or both affecting at least two faces, arms and legs;
✓ Higher cerebral dysfunction (e.g. dysphagia [swallowing disorder], dyspraxia [coordination disorder], neglect, dyscalculia [difficulty in understanding numbers];
✓ Hemianopia homonym.
✓ If consciousness is impaired, dysfunction of the higher cerebral and visual fields is assumed.

- *Partial Anterior Circulation Syndrome (PACS):*

✓ Two of the three components of TACS or higher pure cortical dysfunction, or pure motor or sensory deficits, but not as extensive as lacunar syndrome.

- *Lacunar Syndrome (LACS):*

✓ Pure motor or pure sensory deficits affecting at least two of the face, arms or legs;
✓ Sensorimotor deficits;
✓ Ataxic hemiparesis;
✓ Dysarthria (slurred speech), stiff hands;
✓ Acute onset movement disorder.

- *Posterior circulation syndrome (POCS):*

✓ Isolated heminopia;
✓ Brainstem signs;
✓ Cerebellar ataxia (inability to coordinate balance, gait, extremities and eye movements).

➢ *Epidemiology and Risk Factors*

Asia, home to more than 60% of the world's population and many of its "developing" nations, has a particularly major stroke problem. With the exception of certain nations like

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Japan, stroke mortality is higher in Asia than it is in Western Europe, the Americas, or Australasia. After ischemic heart disease, stroke was the leading cause of death worldwide in 2015, causing 6.3 million deaths. Of these, ischemic stroke was answerable for around 3 million passings, and hemorrhagic stroke caused 3.3 million passings.[9]

Globally, the incidence of strokes has decreased by 21%; however, in the UK, the number of strokes has decreased from 152,000 in 2013 to 100,000 in 2015. Despite this decline, stroke remains the fourth most common cause of death. Considering that there are 100,000 strokes annually in the UK, one stroke occurs every five minutes. One of every eight strokes is deadly inside the initial 30 days, the gamble of repetitive stroke is most prominent in the initial 30 days after a stroke, and 66% of all stroke survivors will have some type of handicap.

Risk factors for stroke are categorized as either modifiable or non-modifiable. Hypertension, diabetes, and smoking are less specific but more prevalent general modifiable risk factors. All of these factors have an effect on health in some way and offer opportunities to alter risk in many individuals. Atrial fibrillation and TIA are two other specific risk factors that are less prevalent. Non-modifiable gamble factors incorporate age (stroke endanger copies each 10 years of life after age 55), orientation (a larger number of men have strokes than ladies; notwithstanding, more ladies pass on from stroke) and hereditary elements (for example Disease of Fabry).

Embolic strokes account for the bulk of ischemic strokes that occur in people with cardiovascular disease. The aorta or heart may be the immediate source of an embolic stroke.

➢ *Pathophysiology*

For the *Trials of Org 10172 in Acute Stroke Treatment* (TOAST), a framework for classifying ischemic stroke subtypes was devised, mostly based on etiology and mechanism leading to vascular occlusion. This information should impact acute and secondary preventive actions, making it crucial for day-to-day management. The most widely used classification, TOAST, includes[9]

- Both extracranial and intracranial arteries may be affected by big vessel **atherothrombosis**, which is defined as the development of lipid-containing atherosclerotic plaques on the inner walls of large blood vessels. The beginning of the vertebral artery, the split in the common carotid artery, and the middle cerebral artery are the most typical locations where atherosclerotic plaque forms. In atheroemboli, a clots structures in the vessel wall, breaks and deliveries bits of clump, which are conveyed downstream and stopped in more modest blood vessel branches, bringing about numerous little strokes an inside the normal area of the parent vessel.
- A blood clot that may have originated inside the heart, broke loose, entered the circulation, and lodged downstream in a cerebral artery is the cause of **cardioembolism**. Intracardiac blood stasis (such as atrial fibrillation) or adherent thrombogenic devices or lesions (such as implanted prosthetic valves) can cause clots to form within the heart.
- The term "**small vessel disease**" describes occlusive disorders affecting the brain's microcirculation. The pons in the middle brain stem, supplied by penetrators originating from the basilar artery; the deep areas of the hemispheric white matter; the internal capsule, a region of white matter proximal to the middle cerebral artery and supplied with blood by its penetrating branches; and the thalamus, which is primarily dependent on branches of the posterior cerebral artery, are common locations for small vessel disease. Small (less than 1.5 cm) infarcts in these areas typically present with one of the classic lacunar syndromes, depending on where they occur in the brain.
- Extracranial artery dissection, nonatheroscleotic vasculopathy, hypercoagulable conditions, and hematologic diseases are among the **other causes** of specific strokes.
- Patients whose full examinations for coagulopathy, intracranial or extracranial major artery stenosis, cardiac conduction abnormalities, and other disorders provide no cause identification are considered to have unknown reasons. About 40% of ischemic strokes have an **unknown origin**. A stroke can be considered cryptogenic after normalized evaluation when clinical assessment and neuroimaging show shallow or huge cerebral localized necrosis, however nothing from what was just mentioned routine vascular, cardiovascular or hematologic tests have uncovered a potential reason for the stroke. Cryptogenic embolism has as of late been named Embolic Stroke of Obscure Source (ESUS).

There is a complex cycle of interrelated molecular and cellular pathways that provide the biochemical basis of the pathophysiological process in cerebral ischemic stroke. When a stroke starts, there is severe focal hyperperfusion (decreased regional blood flow in the irreversible ischemia zone <22 mL/100 g/min). This leads to a number of problems, including increased pCO2, decreased pO2, tissue acidosis, bioenergetic insufficiency, excitotoxicity, oxidative stress that causes additional microvascular damage, activates neuronal and glial cells, and causes leukocytes to migrate through the damaged blood-brain barrier (BBB). Ultimately, through necrosis or apoptotic mechanisms, these cascade responses result in the widespread death of neurons, glial cells, and endothelium.[4]

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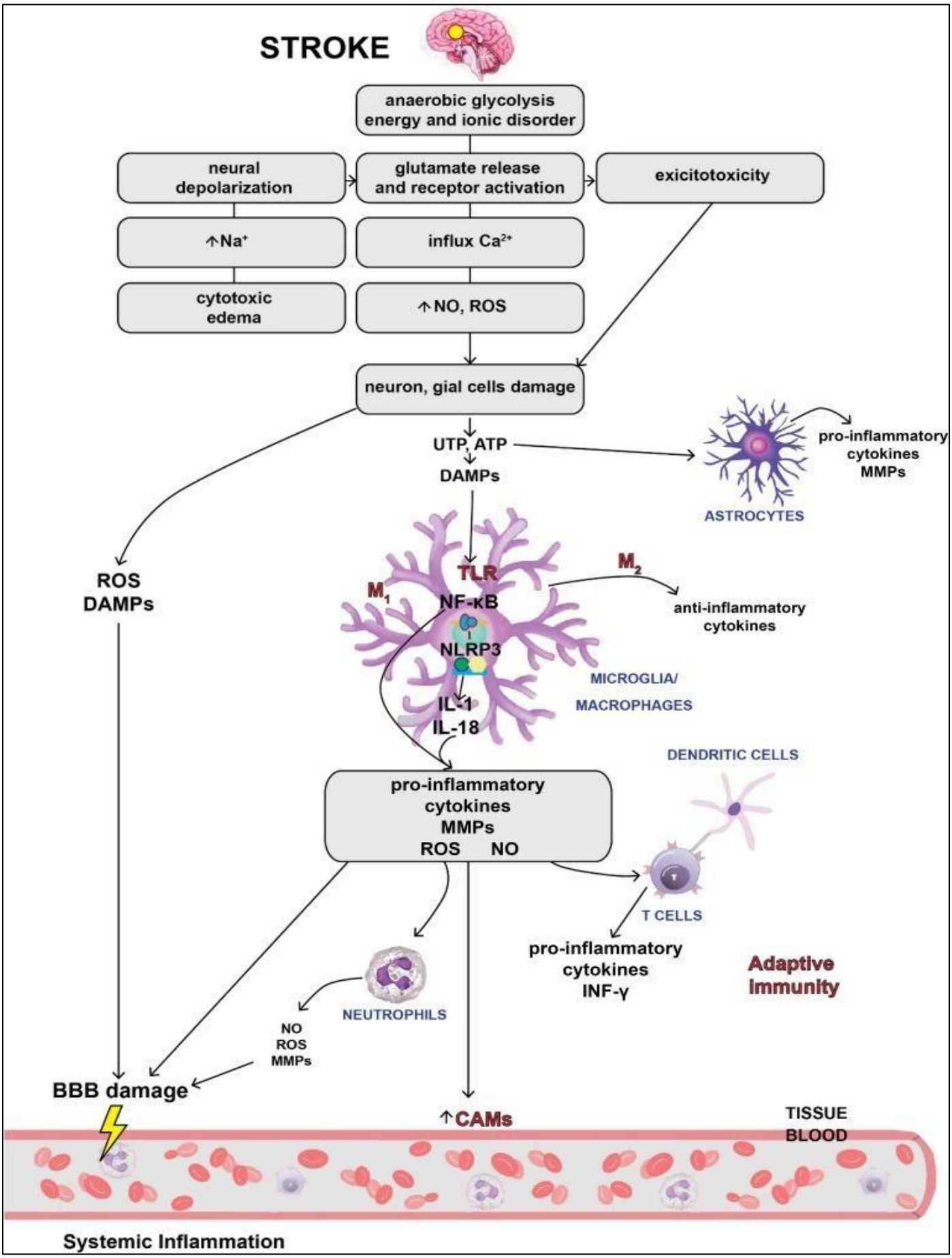

Fig 1 Patomechanism of Acute Ischemic Stroke

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From the point at which the flow stops to the last phases of regenerative processes related to ischemic tissue repair, inflammatory conditions are crucial to the ischemic cascade. In the cerebral infarction region, energy shortage resulting from a loss of neuronal ATP (adenosine triphosphate) synthesis is the primary mechanism of cell death. Na+/K+ - ATPase activity declines, extracellular K+ ion concentration rises, and uncontrollably large amounts of Na+, Ca2+, and Cl-ions enter the cell. Cytotoxic edema develops as a result of the gradual depolarization and loss of membrane potential of the cell membrane, which raise salt inflow and permit osmotic water transfer into the cell. Consequently, the buildup of Na+ and Ca2+ ions causes organelle deterioration, membrane deterioration, and cellular death. Reduced glutamate reuptake is another effect of impaired ATP generation, and high extracellular buildup results in the ischemia death of neurons in the penumbra area. Excitotoxicity and the buildup of Ca2+ ions brought on by overactivation of glutamate receptors result in mitochondrial failure and death. Ca2+ ion inflow stimulates catabolic enzymes by generating arachidonic acid and raising the generation of reactive oxygen species, particularly in neurons.

Increased formation of reactive oxygen species (ROS) permits low molecular weight molecules to flow through the membrane, causing necrosis and, depending on the degree of neuronal injury, programmed nerve cell death. Microglia and astrocytes are stimulated by ROS excitotoxicity and proliferation to release cytokines, chemokines, and matrix metalloproteinases (MMPs). Neutrophils can enter the ischemic area of the brain because these inflammatory mediators cause the expression of cell adhesion molecules on the endothelium surface, such as P-selectin, E-selectin, endothelial-leukocyte adhesion molecule (ELAM-1), and intercellular cell adhesion molecule-1 (ICAM-1). Furthermore, endothelial cells express more chemokines to attract leukocytes to the damaged area. Despite their helpful function, infiltrating immune cells can also cause harm to the ischemic brain by generating a variety of harmful immune cytotoxic mediators, such as NO, ROS, and prostanoids, which lengthen the inflammatory response and worsen brain damage. Additionally, they may result in secondary issues such hemorrhagic transformation and swelling. Constant leukocyte inflow results in lymphocytopenia, which in turn leads to a marked immunodeficiency that raises the risk of infection following a stroke. Furthermore, the autonomic nervous system is activated by an excessive concentration of pro-inflammatory mediators, which inhibits pro-inflammatory pathways and stimulates anti-inflammatory mechanisms by releasing growth factors and interleukins. Moreover, "danger signals" sent by necrotic neurons trigger the immune system and produce molecular patterns (DAMPs). DAMPs cause microglia to develop Toll-like receptors (TLRs), which in turn activate NF-kB to produce the majority of pro-inflammatory cytokines. When caspase-1 is activated by the NLRP3 inflammasome, cytokines IL-1β and IL-18 eventually mature and secrete. Pro-inflammatory cytokines (IL-1β, interleukin 6 (IL-6), IL-18, and tumor necrosis factor (TNF-α)) and chemokines are produced by M1 microglia, whereas anti-inflammatory cytokines (IL-10, IL-4, and transforming growth factor-beta (TGF-β)) are produced by M2 microglia. These cytokines are released several days after acute brain damage and lead to the inhibition of inflammation.[4]

Microglia, astrocytes, and neurons generate MMPs, which cause baseplate degradation, enhance BBB permeability, and make it easier for more peripheral immune cells to enter stroke-affected brain regions. This is due to the fact that acute brain ischemia sets off a systemic immune response in addition to a local inflammatory reaction. Both innate and adaptive immunity play a role during stroke, although they are unaffected during the acute injury phase. However, adjusting adaptive immunity offers novel protective benefits for the ischemic brain and opens up new therapeutic avenues for stroke patients. To fully utilize the therapeutic potential of stroke immunology, a deeper comprehension of the relationship between the immune system and the ischemic brain is necessary. Immunomodulation is not without negative side effects.[4]

B. Interleukin-6 (IL-6)

The pleiotropic cytokine interleukin-6 (IL-6) is generated by both lymphoid and non-lymphoid cells and has a variety of biological functions. Immune reactivation, the acute phase response, inflammation, and hematopoiesis oncogenesis are all regulated by IL-6. Interferon-b2 (IFNb2), T-cell Replacing Factor (TRF), B-Cell Differentiation Factor, 26-kDa protein, B-Cell Stimulatory Factor-2 (BSF2), Hepatocyte-Stimulating Factor (HSF), Hybridoma-Plasmacytoma Growth Factor (HPGF or IL-HP1), and Monocyte- Granulocyte Inducer type 2 (MGI-2) were some of the original names for IL-6. But subsequent investigation showed that each of these molecules is the same.[11]

Leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary inhibitory factor (CNTF), cardiotropin-1 (CT-1), cardiotrophin-like and neurotrophin-1/B-cell stimulating factor 3 (NNT-1) related cytokines, neuropoietin (NPN), IL-27, and IL-31 are all members of the interleukin 6 (IL-6) family of cytokines. With the exception of IL-31, all cytokines of the IL-6 class possess the membrane glycoprotein gp130 as a common subunit for both receptor and signal transducer. First, membrane-attached receptors called IL-6 receptor (IL-6R) or IL-11 receptor (IL-11R) are bound by IL-6 and IL-11, respectively. Then, gp130 is bound by the IL-6/IL-6R or IL-11/IL-11R complex, which forms a gp130-homodimer and initiates the signal. Human herpes virus 8 (HHV-8) also secretes a virus called viral IL-6 (vIL-6), which does not require IL-6R to signal through gp130 homodimers. Via the gp130/LIF-R heterodimeric receptor complex, LIF, CNTF, OSM, CT-1, NPN, and NNT-1 signal. Through a receptor complex made up of OSM-R and gp130, OSM sends signals. Through the gp130/WSX-1 heterodimeric receptor complex, IL-27 carries out its intended activity.[12,13]

The creation of gp130-like receptor (GPL) heterodimers with OSM-R is induced by IL-31, the only IL-6-type cytokine that does not require gp130 receptor chains. Other cytokines of the IL-6 type, like IL-6 and IL-11, also require additional

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specialized receptors, such as soluble Epstein- and glycosylphosphatidylinositol (GPI) for CNTF, CLC, NPN, and NNT-1, in addition to CNTF-R. Gene 3 (EBI-3) induced by the Epstein-Barr virus for p28 (IL-27). Although the gp130/LIF-R heterodimer is the direct mechanism by which CT-1 operates, nerve cells are also thought to contain an as-yet-unidentified CT-1 specific GPI receptor.[14]

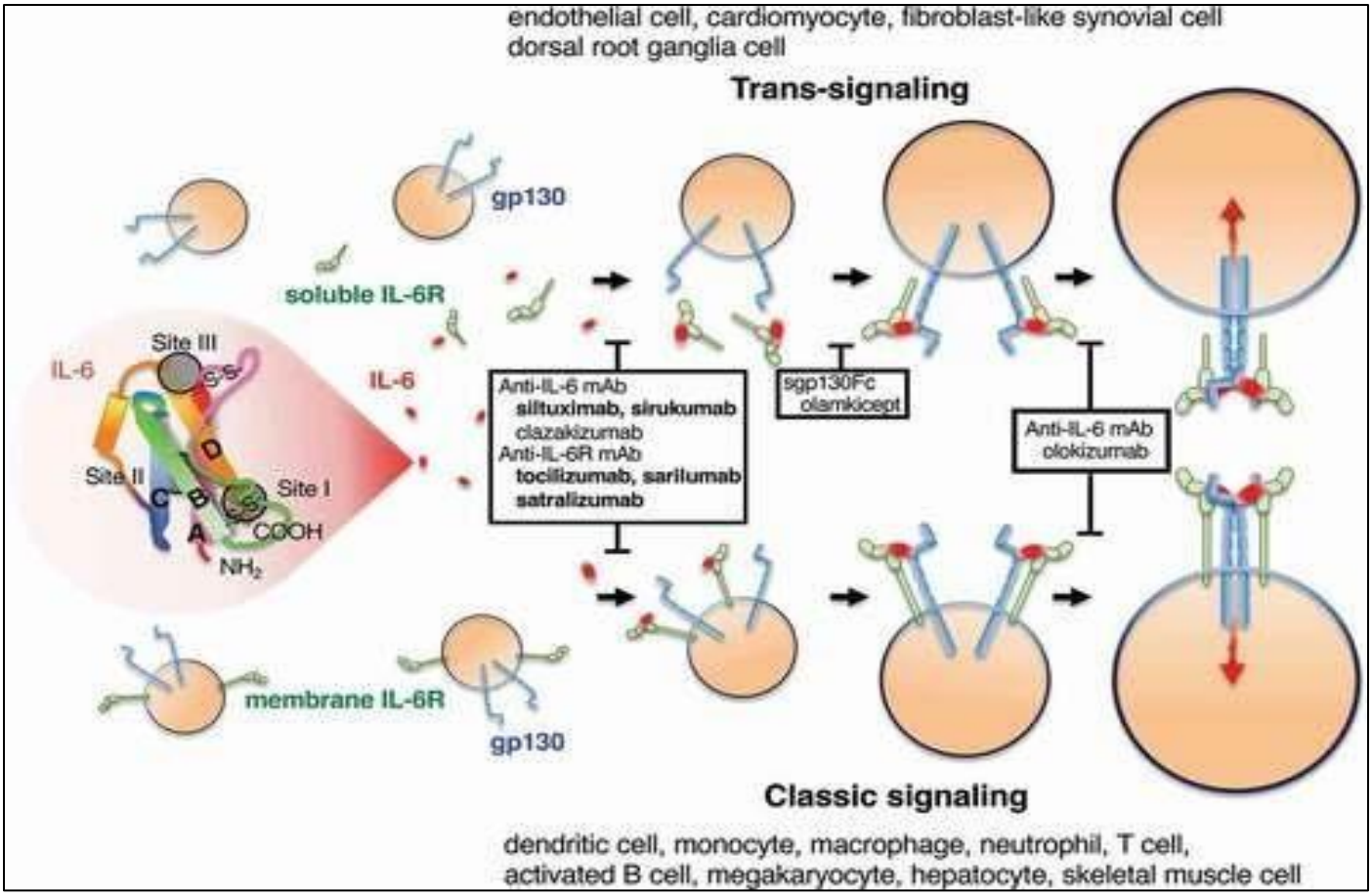

Fig 2 Complex Mechanism of IL-6 Formation

The type I transmembrane glycoprotein IL-6R, also known as CD126 or gp80, and the type I transmembrane signal transducer protein gp130 (also known as CD130) bind to IL-6 to form the receptor complex that mediates the biological activity of IL-6. IL-6 initially attaches to the membrane-bound non-signaling receptor IL-6R (mbIL-6R) on target cells. The JAK/STAT, ERK, and PI3K signal transduction pathways are activated when this IL-6 and IL-6R combination binds to two gp130 molecules, resulting in IL-6 signal transduction.[15]

The 212 amino acids (aa) that make up IL-6, a cytokine with a molecular weight of 21–29 kDa, including a hydrophobic signal sequence located at the N-terminal region. IL-6 must attach to its target receptor, which is made up of the 130 kDa glycoprotein (gp130), which contains the signaling subunit, and the IL-6-specific receptor (IL-6R), which includes the binding subunit, in order to cause a biological response. There are two types of IL-6R that have been discovered: soluble receptor (sIL-6R) and membrane receptor (mIL-6R). The 'classical signaling pathway' is triggered when IL-6 binds to the mIL-6R/gp130 complex. When IL-6 binds to sIL-6R, the complex attaches to membrane-bound gp130, initiating the signaling cascade. Additionally, soluble gp130 (sgp130) binds to the IL-6/sIL-6R complex and functions as a natural inhibitor of IL-6 signal transduction. sIL-6R is an end product of the metallo-endopeptidase ADAM protein. (Prairie, 2021). IL-6R is a glycosylated type I membrane protein weighing 80 kDa. Human IL-6R's Ig-like domain stabilizes the receptor during intracellular trafficking via the secretory pathway, although it is not necessary for IL-6 binding. Residues in IL-6R domains 2 and 3 mediate the binding of IL-6 to IL-6R.[12]

Gp130 is a glycosylated type I membrane protein that ranges in size from 130 to 150 kDa and has six extracellular domains, one transmembrane domain, and a cytoplasmic domain. An N-terminal Ig-like domain (D1), two cytokine-binding domains (CBD), domains 2 and 3, and three fibronectin-like domains (FN III), domains 4-6, are present on Gp130. Apart from their physical connection, gp130 and IL-6R also interact through the binding of gp130's Ig-like domain to IL-6 site 3 and gp130's CBM domain to IL-6 site 2. An interstrand disulfide bond is formed by two pairs of cysteines in the CBM domain, which is found at the N end of domain 2. The Trp-Ser-X-Trp-Ser (WSXWS) motif is conserved in the C-terminal domain at position 3.[16]

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The transfer of the signal to the cytoplasmic domain of gp130 requires the membrane proximal domains, or domains 4-6. Signal transduction activity was either absent or decreased in mutant deletions lacking D4, D5, or D6. Additionally, a study of symmetrical IL-6/IL-6R/gp130-D1-D6 utilizing single-particle electron microscopy showed that the cytokine gp130 binding domain's COOH-terminal portion is around 100. The transmembrane domain of the cell surface-expressed receptor is closely aligned due to the close proximity to the COOH-terminal region of the membrane-proximal fibronectin III domain, which enables the activation of intracellular signaling. The signaling complex is quickly internalized upon ligand binding, which is facilitated by a dileucine-like motif in the gp130 cytoplasmic domain.[17,18]

Leukocytes move from blood vessels to wounded tissue as part of the intricate defense system known as inflammation, where they eliminate substances that may cause further tissue damage. While chronic inflammation is a long-lasting phenomena that can result in tissue damage, acute inflammation is a limited helpful response, particularly under viral challenges. One characteristic of acute inflammation is the initial predominance of neutrophils in the leukocyte infiltrate, which gives way to monocytic cells within 24 to 48 hours. On the other hand, the histology of persistent inflammation identifies the presence of mononuclear cells such lymphocytes and macrophages.[19,20]

Acute phase response encompasses a range of behavioral, physiological, metabolic, and nutritional alterations in addition to variations in the concentration of several plasma proteins, also referred to as acute phase proteins. Acute phase proteins are a group of plasma proteins that, in inflammatory illnesses, either decline by 25% in the case of negative acute phase proteins or rise by 25% in the case of positive acute phase proteins. Acute phase protein synthesis by hepatocytes is a major factor in fluctuations in acute phase protein concentrations. (Gitlin, 1987). Acute phase protein synthesis is stimulated by cytokines generated during and engaged in the inflammatory process. IL-6, IL-1β, interferon, transforming growth factor-β, tumor necrosis factor-α, and IL-8 are some of the cytokines linked to inflammation. Although several cell types can create these cytokines, macrophages and monocytes at the site of inflammation are the main producers.[21]

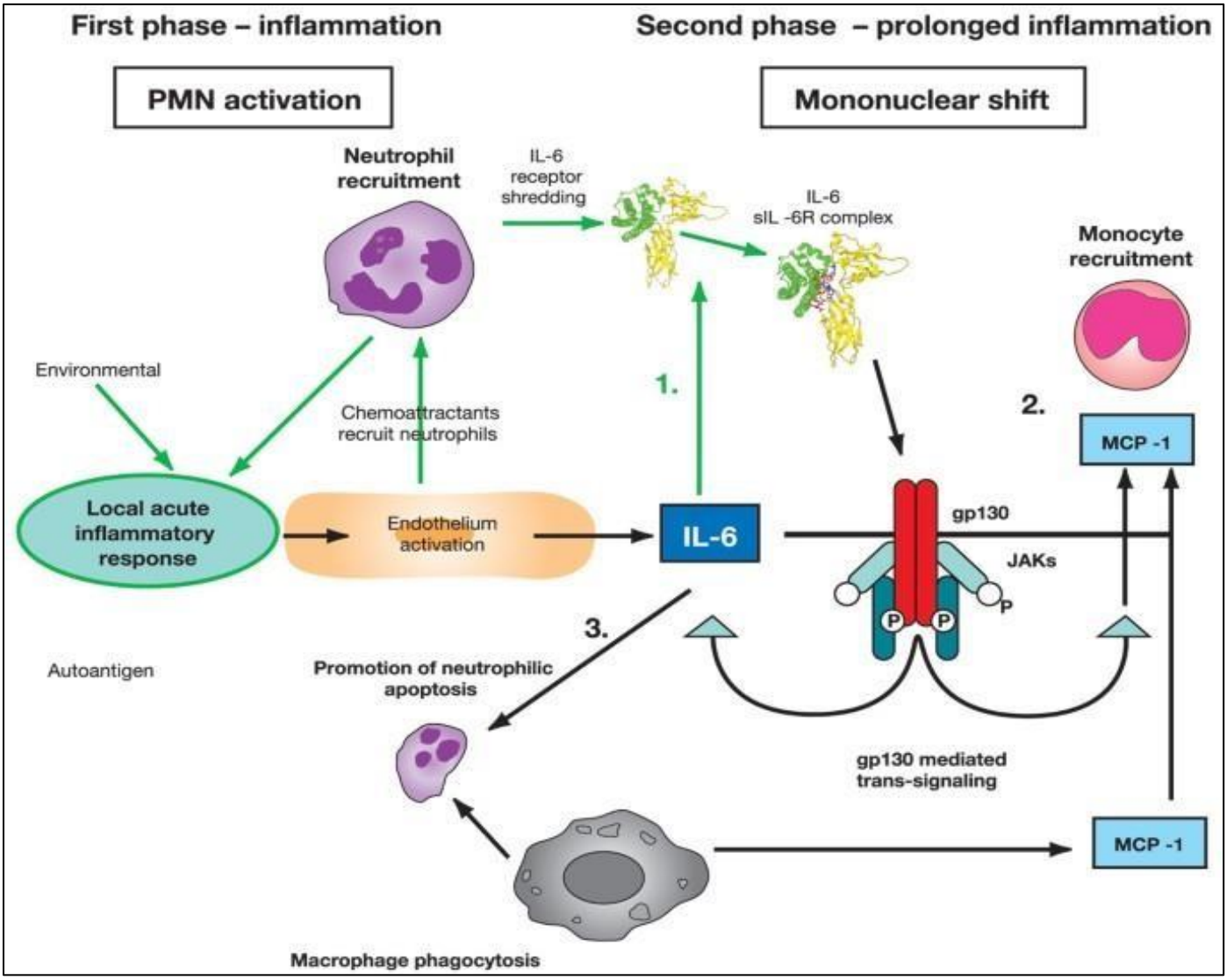

Fig 3 IL-6-Influenced Inflammatory Mechanism

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The production of acute phase proteins is stimulated by certain cytokines, particularly IL-6, in response to different stimuli. In various inflammatory diseases, there are differences in the pattern of cytokine production and acute phase response. Acute phase shifts have long been utilized as a clinical guide for diagnosis and treatment because they show the existence and degree of inflammation. IL-6 plays a crucial role in inducing acute phase reactions as well as cellular immune responses to the affected cells and mucosal humoral responses meant to prevent reinfection in chronic diseases, which are typically characterized by immune stressors such as tumors and chronic intracellular infections.[22]

The inflammatory response needs to trigger an immune response and eliminate the harmful chemical quickly and locally in order to fulfill its intended purpose. This is accomplished via a convoluted chain of events that include movement, death, and recruitment of local leukocytes. The switch from neutrophil to monocyte recruitment facilitates the inciting agent's effective elimination through the combined phagocytotic and destructive actions of inflammatory macrophages and neutrophils. However, by eliminating neutrophils and triggering an immunological response, this shift also helps to resolve inflammation.[22]

Apart from inducing the acute phase, IL-6 also leads to the development of particular humoral and cellular immune responses, such as T cell activation, immunoglobulin production, and end-stage B cell differentiation. The primary factor that causes inflammation to change from acute to chronic is the attraction of monocytes to the site of inflammation. The shift from acute to chronic inflammation depends on IL-6. Humans only express a little amount of IL-6Rα on leukocyte and hepatocyte membranes, but soluble forms of the protein can be liberated from neutrophil membranes and are present in high amounts in neutrophil-enriched inflammatory fluids. By binding to gp130 on stromal cell membranes, sIL-6Rα and IL-6 combine to activate these cells in a process known as trans-signalling.[24,25]

In inflammation, the IL-6/IL-6Rα combination promotes the change from neutrophils to monocytes. MCP-1 is predominantly produced by neutrophils that have been primed with inflammatory cytokines for a few hours. When proinflammatory molecules activate endothelial cells, leuko-endothelial adhesion molecules are expressed and platelet-activating factors, IL-8 and IL-6, are secreted. Chemoattractants that originate from the endothelium or other cell sources draw in neutrophils and cause their membranes to produce IL-6Rα. When IL-6Rα and IL-6 are combined, gp130 on the endothelial cell membrane can be ligated, and endothelial (or stromal) cells secrete more IL-6 and MCP-1, which promotes the shift in recruitment from neutrophils to monocytes. Leukocyte infiltration is regulated by IL-6 signaling via sIL-6Rα. Research conducted in vitro verifies that events mediated by sIL-6Rα control the expression of adhesion molecules and chemokines. As a result, IL-6 trans-signaling regulates mediators that help to reduce inflammation.[26]

An essential part of the pathophysiology of acute ischemic stroke (AIS) is the inflammatory response. It has been observed that stroke patients have greater plasma levels of several inflammatory markers than people in the general population.27 Several evaluations indicate that there are distinct patterns of immunoinflammatory activation in respect to the stroke subtypes, based on the pathophysiological variations amongst the subtypes. Following an ischemic or hemorrhagic stroke, a nonspecific systemic inflammatory response takes place as a part of the process of brain injury. When it comes to ischemic stroke, higher levels of inflammatory markers like interleukin-6 and C-reactive protein (CRP) are linked to a worse prognosis. Prostaglandin E2 is released from the brain in response to interleukin-6, and it activates the hypothalamus, raising body temperature. As a result, early and prolonged elevations in interleukin-6 in CSF and blood most likely correspond with an increased risk of fever that worsens tissue damage after ischemic stroke. Various studies have shown that fever associated with greater infarct size and poor stroke prognosis.[28]

In acute stroke, IL-6 expression is influenced by both hereditary factors and infarct size. Due to linkage disequilibrium, the IL-6 promoter has four polymorphic regions that are linked to eight frequent haplotypes. Our group of sick and control people had a similar haplotype distribution to other white samples.[29] Only the allelic frequency of the uncommon haplotype C (G-G-10/10-G) separated patients from control subjects; nevertheless, a larger sample size is needed to confirm the haplotype C's link to cerebrovascular disease. Low IL-6 levels in stroke patients are linked to the most prevalent haplotype of the IL-6 promoter (A-G-8/12-C), F. It is well known that the IL-6 promoter controls the production of IL-6 in neuronal cells in response to adenosine and other stimuli related to cerebral ischemia.[30] This implies that either non-F haplotypes prefer IL-6 induction or that the mix of polymorphisms seen in F haplotypes may interfere with IL-6 induction in stroke. It is evident that IL-6 promoter haplotypes in astrocyte-like cells are necessary for the stimulation of IL-6 gene transcription by adenosine analogs, which are implicated in ischemia pathogenesis. In vitro, haplotype F only mediates low induction of IL-6 gene transcription, whereas haplotypes B and E produce substantial induction.[31]

Following a stroke, a prolonged inflammatory response may set off neurotoxic pathways that eventually result in degeneration. Neuroinflammation-mediated illnesses may also be made worse by damaged neurons, as they can produce chemokines and activate astrocytes and microglia. Hypoperfusion brought on by a stroke may exacerbate oxidative stress and endothelial damage, which in turn may hasten or worsen neuroinflammation, disruption of the blood-brain barrier, and neurodegeneration. There is also a hypothesis that IL-6 produced systemically could penetrate the blood-brain barrier and harm the brain. This theory is supported by experimental research, which shows that mice with central nervous system overexpression of pro-inflammatory cytokines exhibit neurodegeneration and cognitive impairment.[32,33]

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III. CONCLUSIONS

Although the etiology of stroke is complicated, oxidative stress and inflammatory responses are believed to be important processes causing damage to the neurons. Numerous factors also contribute to the development of inflammation in stroke patients, with hereditary genes responsible for inflammatory reactions playing a significant role. Furthermore, research has demonstrated that numerous genes may influence the etiology of stroke, the extent of the ischemic area, and ultimately the patient's prognosis.

The pleiotropic cytokine interleukin-6 (IL-6) is generated by both lymphoid and non-lymphoid cells and has a variety of biological functions. Immune reactivation, the acute phase response, inflammation, and hematopoiesis oncogenesis are all regulated by IL-6. The production of acute phase proteins is stimulated by certain cytokines, particularly IL-6, in response to different stimuli. Under various inflammatory situations, there are variations in the pattern of cytokine production and acute phase response. In order to fulfill its purpose, the inflammatory response needs to quickly and locally eliminate the harmful chemical while triggering an immunological response..

An essential part of the pathophysiology of acute ischemic stroke (AIS) is the inflammatory response. When it comes to ischemic stroke, higher levels of inflammatory markers like interleukin-6 and C-reactive protein (CRP) are linked to a worse prognosis. Prostaglandin E2 is released in response to interleukin-6 in the brain, and prostaglandin E2 stimulates the hypothalamus, raising body temperature. In acute stroke, IL-6 expression is influenced by both hereditary factors and infarct size. Due to linkage disequilibrium, the IL-6 promoter comprises four polymorphic regions linked to eight frequent haplotypes. The way in which IL-6 affects post-stroke cognition is still unknown. Following a stroke, a prolonged inflammatory response may set off neurotoxic pathways that eventually lead to degeneration. By releasing chemokines and stimulating astrocytes and microglia, damaged neurons may also make neuroinflammation-mediated illnesses worse.

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