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Pathomechanism and Potential of Mononuclear Therapy for Sensorineural Hearing Loss Post *S. suis* Meningitis

I Nyoman Tri Pramartha[1], AA Raka Sudewi[2], Ni Made Adi Tarini[3], Ni Made Susilawathi[2]

[1]Biomedical Science, Postgraduate Study Program, Udayana University, Bali, Indonesia
[2]Department of Neurology, Faculty of Medicine, Udayana University/Prof. dr. IGNG Ngoerah General Hospital, Bali, Indonesia
[3]Department of Clinical Microbiology, Faculty of Medicine, Udayana University/Prof. dr. IGNG Ngoerah General Hospital, Bali, Indonesia

Corresponding Author: I Nyoman Tri Pramartha

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ABSTRACT

Permanent sensorineural hearing loss (SNHL) is a major morbidity caused by *Streptococcus suis* (*S.suis*) meningitis. The underlying pathomechanism for the occurrence of SNHL are the release of Pore-forming Toxin by *S.suis*, impaired immune regulation, and microcirculation disturbance in patients, which damages cochlear hair cells and spiral ganglion neurons (SGN). This morbidity causes social and economic impacts on patients who are young and productive adult patients. Conventional therapy is still limited in preventing or restoring auditory function, current development studies are toward to cell-based therapies, one of which is mononuclear from bone marrow (BMMNCs) and peripheral blood (PBMNCs). The proposed neurorestorative potential of mononuclear cell-based therapy are through immunomodulation, angiogenesis stimulation, and nerve tissue regeneration. This literature review aims to summarize information on the pathomechanism of SNHL due to *S.suis* meningitis and the proposed neurorestorative potential of mononuclear cell-based therapy for SNHL post *S.suis* Meningitis.

Keywords: *S.suis* meningitis, mononuclear cells, sensorineural hearing loss, therapy

INTRODUCTION

Streptococcus suis (*S.suis*) infection prevalence reported to reach 1500 cases per year globally, with the majority originating from Southeast Asia. This infection can cause meningitis and one of the complication in meningitis is sensorineural hearing loss (SNHL) with an incidence of 9 to 31.6%.[1,2] The worsening of SNHL can cause social impacts such as discrimination, decreased self-confidence and economic disruption in work activities, especially in young and productive adult patients.[3] SNHL complications due to this infection tend to be bilateral, persistent, and dominant at high frequencies, with the main targets of damage to hair cells and spiral ganglion neurons (SGN) of the cochlea.[4]

Cell-based therapies such as mononuclear are therapies developed in the last decade as a neurorestorative strategy.[5] Among potential candidates, bone marrow-derived mononuclear cells (BMMNCs) and

peripheral blood (PBMNCs) are mononuclear cells with immunomodulatory and angiogenesis-stimulating capabilities.[6] Despite their great potential, reviews evaluating their effectiveness in relation to SNHL post-meningitis *S.suis* are not yet available. This literature review was compiled to fill the literature gap and is expected to be a foundation for the development of neurorestorative research with cell-based therapies in the future.

LITERATURE REVIEW

PATHOMECHANISM OF SNHL DUE TO MENINGITIS

Sensorineural hearing loss (SNHL) caused by *S.suis* meningitis is initiated by the action of pore-forming toxins such as suilysin (SLY), which damage endothelial and neural cell membranes, disrupt the blood-labyrinth barrier, and trigger Ca^{2+} influx leading to mitochondrial dysfunction and apoptosis of spiral ganglion neurons (SGN) as the primary sensory cells of hearing. Beyond direct cytotoxicity, the infection induces systemic and local immune dysregulation characterized by NLRP3 inflammasome activation, increased IL-1β, IL-6, and TNF-α, and NF-κB–mediated cytokine cascades that exacerbate cochlear inflammation and barrier permeability. Excessive neutrophil infiltration and NETosis further aggravate tissue injury through oxidative stress and protease release. In parallel, vascular endothelial damage and microthrombosis impair cochlear microcirculation, resulting in ischemia, edema, and hypoxia that disrupt ionic homeostasis and worsen neuronal and hair cell degeneration as illustrated in Figure 1.

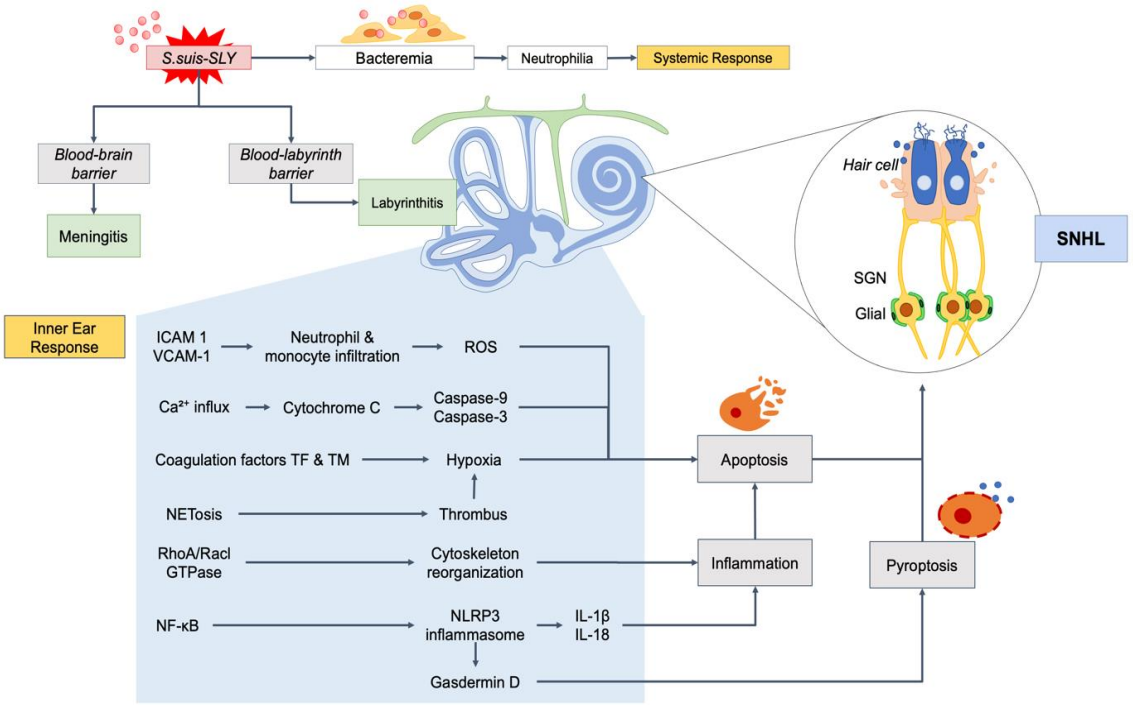

Figure 1. Proposed pathomechanism of *S.suis* and SLY toxin causing post-meningitis SNHL

Pore-forming Toxins as Initiators of SNHL

The route of bacterial spread in the brain is through the cerebrospinal fluid and through the cochlear aqueduct, causing purulent labyrinthitis that penetrates the blood-labyrinth barrier (BLB). One of the main factors that initiates this damage is suilysin (SLY),[7] a cholesterol-dependent cytolysin (CDC) that can form pores in the membranes of endothelial cells and nerve cells.[8] Suilysin not only destroys cells mechanically but also triggers barrier dysfunction including the blood-brain and

blood-labyrinth barriers, allowing toxins and immune cells to enter the cochlea.[4,7] Administration of non-cytotoxic sublytic concentrations of SLY in vitro has shown the activation of RhoA/Rac1 GTPase which reorganizes the cytoskeleton through actin changes, increasing bacterial paracellular permeability and further inflammatory responses.[9]

The primary damage occurs in the spiral ganglion neuron (SGN), as the primary sensory neuron that transduces sound signals from hair cells to the cochlear nucleus in the brainstem, precisely at the junction of the pons and medulla. The regeneration capacity of SGN is very low and if damage occurs in cases of SNHL, it is generally irreversible.[10] Studies in patients with meningitis confirmed by *S.suis* infection who underwent cochlear implant (CI) showed significantly higher electrode impedance and neural response telemetry (NRT) thresholds than in cases of meningitis caused by non-*S.suis*, indicating deep and extensive SGN damage because a higher stimulus is required by CI to be able to induce a response in nerve cells.[11] Early SGN damage will interrupt the transmission pathway, resulting in impaired hearing even though the hair cells are relatively intact.[12] However, worsening SGN damage can continue to the hair cell structure. If the inflammatory response continues to increase, hair cells will also eventually undergo apoptosis and worsen the hearing deficit in patients.

Pore-forming by SLY increases the permeability of the cell membrane, allowing large amounts of ions, especially Ca^{2+}, to influx into the cytoplasm. Excessive accumulation of Ca^{2+} ions trigger disruption of intracellular homeostasis.[13] High intracellular Ca^{2+} levels disrupt mitochondrial function, causing the opening of the mitochondrial permeability transition pore, which subsequently increases the release of cytochrome c from the mitochondria to the cytoplasm. The release of cytochrome c acts as a signal that activates the intrinsic apoptosis pathway through the activation of caspase proteins, namely caspase-9 and caspase-3, thus leading to apoptosis.[14]

Impaired Immune Regulatory Cause Cochlear Damage

Streptococcus suis infection in the early stages will spread through bacteremia and cause a systemic inflammatory reaction. Retrospective studies have evaluated that systemic inflammatory markers, NLR (neutrophil-to-lymphocyte ratio) is positively correlated with the severity and prognosis of SNHL, indicating that systemic immune reactions also has potential to determine the degree of cochlear lesions.[15] Although there is no specific data related to *S.suis*, an inflammatory pattern in the form of increased neutrophils is found in meningitis patients due to other bacteria that lead to SNHL, [16] so this mechanism is very reasonable as a theoretical basis for markers of SNHL progression after meningitis suis and needs to be studied for future evaluation.

The local immune response in the inner ear in *S.suis* infections causing meningitis indirectly contributes to cochlear damage. Although the cochlea is considered an immune-privileged site, it is now known that resident immune cells such as macrophages and perivascular melanocyte-like macrophages (PVM/Ms) reside within the cochlear structures, namely the spiral ligament and stria vascularis, which play an important role in homeostasis regulation.[17] Danger signals generated by toxins and tissue damage activate the NLRP3 inflammasome, a pro-inflammatory protein complex formed in cochlear macrophages. The components of the NLRP3 inflammasome consist of the cytosolic sensor NLRP3, the adaptor ASC, and the protease caspase-1. When activated, caspase-1 cleaves the pro-inflammatory cytokine precursors pro-IL-1β and pro-IL-18 into their active forms (IL-1β, IL-18) to be secreted into the cochlear environment and triggers the cell death process pyroptosis via the gasdermin D protein.

These cytokines bind to their receptors (IL-1R1 and IL-18Rα/β) amplifying the local inflammatory response and inducing the release of the cytokine IL-6. Activation of the NLRP3 inflammasome has been shown to be involved in various conditions of sensorineural hearing loss (SNHL), ranging from auto-inflammatory diseases, infections, noise exposure, to ototoxic medications.[18]

Endothelial injury due to inflammation causes cell dysfunction, thus increasing the expression of adhesion molecules (ICAM-1, VCAM-1) which facilitates the infiltration of leukocytes such as monocytes and neutrophils from the circulatory system into the perilymph and endolymph. Neutrophils produce reactive oxygen species (ROS) and protease enzymes (myeloperoxidase, elastase) which play a dual role, namely the destruction of pathogens and also body parts, namely hair cells, supporting cells, and SGN through a bystander effect mechanism. [19,20] Shortly after invasion of brain and inner ear tissue, NF-κB activation occurs. NF-κB transcription factors play a role in regulating various pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, as well as chemokines that induce neutrophil migration to the inflammatory area.[21] Similar findings were also shown in the *S.suis* infection model by intraperitoneal injection, there was an increase in NF-κB levels in the blood and brain of experimental animals which reached a peak on the 3rd day post-infection. NF-κB activation enhances the release of inflammatory mediators that increase barrier permeability and cause leukocyte infiltration, particularly neutrophils.[22]

Microglia are the primary resident immune cells in the central nervous system that undergo significant activation in response to bacterial invasion and local inflammation.[23] Immunohistochemical studies have found that microglia experience increased density, morphological changes to an active amoeboid form related to phagocytic activity, and proinflammatory mediators to protect and restore the brain from infection.[22] However, on the other hand, excessive microglia activation creates a toxic environment for hair cells and SGNs.[24]

Microcirculation Disturbance Inhibit Cochlear Recovery

The cochlea is a sensory organ that is sensitive to changes in blood supply. Blood flow in structures such as the stria vascularis, spiral ligament, and modiolus plays a vital role in maintaining ionic homeostasis and metabolism of sensory cells, including hair cells and SGNs.[17] During severe infections such as meningitis caused by *S.suis*, microcirculatory function can be significantly impaired, leading to local ischemia, edema, and ultimately degeneration of the auditory tissue. Post-infectious cochlear vascular damage can occur directly by bacterial invasion or through the release of inflammatory mediators that cause endothelial dysfunction. Studies have reported that meningitis can cause the breakdown of microvessel integrity in the CNS and cochlea with increased capillary permeability and immune cell infiltration. A study by Jafarzadeh et al., showed that increased inflammatory factors after cochlear ischemia play a significant role in reducing hearing sensitivity, and that hearing function improves as the concentration of inflammatory factors in the cochlea decreases. This vascular damage triggers a cycle of inflammation, edema, and oxidative stress that directly impacts hair cells and spiral neurons.[25]

Microthrombosis and small artery spasm due to the inflammatory response worsen the local blood flow supply, creating a hypoxic environment in the cochlea that is very unfavorable for SGN survival. Animal models and the findings of Olivetto et al., clarify that hypoxia and ischemia cause decreased microcirculation, damage to vessel structures in the stria vascularis, and activation of the coagulation pathway through increased expression of tissue factor (TF) and thrombomodulin (TM) in the

vascular endothelium, basal cells of the stria vascularis, hair cells, and pillar cells of the organ of Corti. These circulatory changes trigger microthrombus formation that worsens the injury and disrupts cochlear metabolism. Vascular damage in the basal cells of the stria vascularis causes disruption of the K+ cycle that leads to phosphorylation of JNK, which induces cell apoptosis [26] and activates the NLRP3 inflammasome complex, which exacerbates inflammation.[27] Hypoxic conditions support the body to carry out vascular compensation in the form of angiogenesis and vasculogenesis. The main factors that play a role in this process are vascular endothelial growth factor (VEGF) and fibroblast growth factors (FGF) by pericytes, a proangiogenic cytokine that trigger the growth of new blood vessels and improve local circulation in the cochlea. [28,29]

The active NF-κB inflammatory pathway stimulates neutrophils to release neutrophil extracellular traps (NETs) composed of DNA fragments, histones, and granular proteins.[30] Experimental studies in mice have shown that activation of Nuclear Factor kappa-B (NF-κB), NETs, and microglia activation are important factors in the inflammatory mechanism of *S.suis* infection.[22] This NETosis process is a defense system against pathogens, but on the other hand, it also causes damage to surrounding tissue that has the potential to worsen inflammation.[29,30] Research by Susilawathi et al., showed a significant increase in NET levels in the brains of mice infected with S.suis, with a peak on days 3 and 5, related to neutrophil infiltration and the degree of inflammation.[22] The release of NETs also worsens cell membrane damage in the cochlea, either directly through proteases or through increased oxidative stress, on the other hand, excessive production of NETs also has the potential to form thrombi, especially in sepsis conditions which cause circulatory disorders around the lesion.[30]

Mononuclear Cell-Based Therapy in SNHL

Bone marrow mononuclear cells (BMMNCs) and peripheral blood mononuclear cells (PBMNCs) are increasingly being studied as regenerative agents in various models of nervous system disorders, both in humans and experimental animals. The main mechanisms underlying their potential include the secretion of neurotrophic factors, modulation of the immune response, and stimulation of angiogenesis and neurogenesis, thus supporting nerve tissue repair after injury or degenerative disease. These mechanisms are illustrated in Figure 2.[31,32]

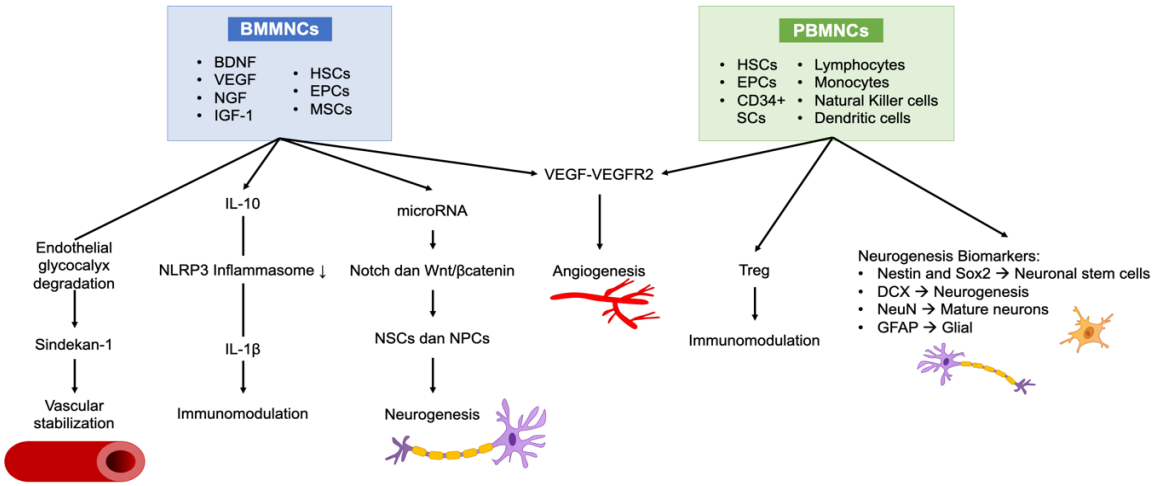

Figure 2. Potential mechanisms of BMMNCs and PBMNCs as mononuclear therapy in SNHL

The components of BMMNCs include hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), and mesenchymal stem cells (MSCs). Regarding neurorestorative potential, BMMNCs can secrete growth factors such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), nerve growth factor (NGF), and insulin-like growth factor-1 (IGF-1).[32,33] These molecules play an important role in cell survival, differentiation, neurite growth and axon regeneration around the lesion. Studies in in vitro and in vivo models of brain injury and stroke have shown that BMMNCs transplantation can increase angiogenesis and neurogenesis, and reduce brain infarction area through autocrine/paracrine effects and direct cell-to-cell interactions through gap junctions.[34]

The SNHL model due to cochlear ischemia in Gerbils showed that BMMNCs injection into the femoral vein after 30 minutes showed significant results in preventing progressive hair cell loss and improving hearing thresholds based on ABR (auditory brainstem response) examination at 8, 16, and 32 kHz. These cells were found to persist in the area of the cochlear spiral blood vessels and did not differentiate into sensory components, but provided support through paracrine effects.[6] The support provided was confirmed in a mouse model with sepsis, where the level of syndecan-1, a marker of endothelial glycocalyx degradation that plays a role in stabilizing vascular structures, was lower in the group given BMMNCs compared to the control.[35] This indicates the vasculoprotective effect of BMMNCs.

Exosomes produced by MSCs, a component of BMMNCs, in peripheral nerve injuries have shown significant effects in enhancing nerve fiber regeneration and remyelination. The combination of exosomes with bioengineering scaffolds has also been shown to accelerate the recovery of neurological function.[36] The release of the anti-inflammatory cytokine IL-10 helps inhibit the inflammatory pathway mediated by the NLRP3 inflammasome and IL-1β, thereby reducing the excessive inflammatory response around the lesion.[18,27] Exosome secretion carries microRNAs and proteins that can influence neurogenesis through the Notch and Wnt/βcatenin pathways, thereby activating neural progenitors.[5] The effectiveness and safety of the intervention, even though the cells are autologous, still require further research to validate the findings and clinical recommendations.

Research from Shah et al., provides a comparison of BMMNCs and PBMNCs in triggering angiogenic responses. In an avian animal model, only PBMNCs were able to form tubular capillary structures that resemble blood vessels, while BMMNCs showed a more multipotent differentiation ability through MSCs components but with a lower angiogenic capacity. The mechanism of angiogenesis can be induced through the VEGF-VEGFR2 pathway.[37] Specific data comparing the angiogenic response by BMMNCs and PBMNCs in the cochlea with mammalian models are currently not available. The majority of data comes from ischemic models in the extremities or the CNS. Therefore, a translational approach is needed to understand how the microvascular response in the cochlea is related to post-meningitis SNHL in mammals.

The components of PBMNCs include lymphocytes, monocytes, natural killer cells (NK cells), and dendritic cells, while the cell fractions in the form of erythrocytes and granulocytes (neutrophils, basophils, and eosinophils) are eliminated during the centrifugation process.[38] Stem cells (SCs) components were also found, namely HSCs, EPCs, and CD34+ SCs.[31] In vitro studies confirmed that PBMNCs interactions can promote hNSC proliferation and differentiation. Zhang et al., proved that PBMNCs significantly increased the expression of proliferation and differentiation markers such as nestin, Sox2, DCX, NeuN, and GFAP in hNSCs, while decreasing the pro-inflammatory immune T

subpopulation and increasing Tregs and anti-inflammatory cytokines.[39] This indicates the potential of PBMNCs to support neurorestoration mechanisms through immunomodulation pathways, paracrine effects, and stimulation of neuronal progenitor proliferation and maturation pathways. In adulthood, neural stem cells (NSCs) and neural progenitor cells (NPCs) remain present in the brain, although neurogenesis activity declines significantly compared to developmental stages. In adult mammals, the two main areas that continue to actively produce new neurons are the subventricular zone (SVZ), located along the lateral wall of the lateral ventricle, and the subgranular zone (SGZ) in the dentate gyrus of the hippocampus. In the SVZ, NSCs/NPCs form a complex niche network with astrocytes, ependymal cells, and microglia, where, when appropriately stimulated, they can proliferate and differentiate into transit amplifying cells (type C), neuroblasts (type A), and ultimately into mature neurons or glial cells.[40] Clinical studies in patients with diabetic peripheral arterial disease have shown that PBMNCs improve the perfusion index of initially ischemic tissue. This indicates an angiogenic effect and microcirculation improvement.[41] This effect is relevant in cases of post-meningitis SNHL, where impaired cochlear circulation is a major contributor to permanent SGN damage.

Challenges and Recent Study Developments

The main challenges in the development of mononuclear cell-based regenerative therapy for neurological disorders, especially SNHL, lie in the variability of individual biological responses, limitations of translational models from animals to humans, safety aspects including long-term side effects that may arise.[5,18,39,40] Future studies need to integrate the evaluation of local and systemic inflammatory biomarkers, as well as the evaluation of vascular damage to obtain a comprehensive picture of the mechanisms of cochlear damage and recovery, while optimizing cell-based therapy strategies.

CONCLUSION

Mononuclear cell-based therapies, particularly BMMNCs and PBMNCs, have the potential to be restorative solutions for SNHL caused by *S.suis* meningitis through immunomodulation, angiogenesis, and stimulation of neuroregeneration. This literature review is limited by the available studies related to long-term clinical evidence and validation of therapy protocols, so further studies are needed to ensure their effectiveness and safety as future therapies for SNHL post-*S.suis* meningitis.

Declaration by Authors

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