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Immunological mechanisms in post-stroke dementia

Kristian P. Doyle, PhD^{1,*}, Marion S. Buckwalter, MD PhD^{2,*}

¹Departments of Immunobiology and Neurology, University of Arizona

²Departments of Neurology and Neurological Sciences, and Neurosurgery Stanford School of Medicine

Abstract

Purpose of review: To review new evidence on links between post-stroke dementia and inflammation.

Recent findings: Although there are still no treatments for post-stroke dementia, recent evidence has improved our understanding that stroke increases the risk of incident dementia and worsens cognitive trajectory for at least a decade afterwards. Within approximately the first year dementia onset is associated with stroke severity and location, while later absolute risk is associated with more traditional dementia risk factors such as age and imaging findings. The molecular mechanisms that underlie increased risk of incident dementia in stroke survivors remain unproven, however new data in both human and animal studies suggests links between cognitive decline and inflammation. These point to a model where chronic brain inflammation, provoked by inefficient clearance of myelin debris and a prolonged innate and adaptive immune response, causes post-stroke dementia. These localized immune events in the brain may themselves be influenced by the peripheral immune state at key times after stroke.

Summary: This review recaps clinical evidence on post-stroke dementia, new mechanistic links between the chronic inflammatory response to stroke and post-stroke dementia, and proposes a model of immune-mediated neurodegeneration after stroke.

Keywords

Inflammation; stroke recovery; post-stroke dementia

Introduction

Stroke approximately doubles the risk that a person will be diagnosed with dementia later in life. The risk is highest in the six months after stroke but an increased risk persists for at least a decade, even after controlling for known dementia risk factors [1–4]. Dementia risk is

*Co-Corresponding Authors: Kristian P. Doyle, PhD, Associate Professor, Depts. of Immunobiology and Neurology, Arizona Center on Aging & BIO5 Institute, University of Arizona, Tucson, AZ, 85724, Phone: 520-626-7013, doylekr@email.arizona.edu, Marion S. Buckwalter, MD PhD, Associate Professor, Depts. of Neurology and Neurological Sciences, and Neurosurgery, Wu Tsai Neurosciences Institute, Stanford School of Medicine, 1201 Welch Rd, P209, Stanford, CA, 94305-5489, Phone: 650-724-9098, marion.buckwalter@stanford.edu.

Conflicts of interest

The authors have no conflicts of interest.

highest for hemorrhagic strokes, including subarachnoid hemorrhage, and less for ischemic stroke, with hazard ratios (HR) ranging from 1.6 to 2.5 [4]. Hazard ratios are higher for young adult stroke victims (about 7), then decrease with aging, while the absolute risk of incident dementia increases with age [4]. This drop in relative dementia risk likely occurs because the risk of dementia from other causes rises with age. The molecular mechanisms whereby stroke increases a person's risk of later getting dementia are unknown, and because of this there are no potential treatments or methods for determining whether an individual's dementia is due to their stroke or other causes.

Risks and biphasic trajectory of dementia risk after stroke

In addition to age, larger stroke size is associated with incident dementia after stroke, particularly within the first year. Pendlebury et. al. recently stratified the risk of incident dementia by stroke severity in a large community cohort, OxVasc [2]. In participants with no pre-existing dementia, the risk of new dementia during the first year after stroke was 34% in those with severe stroke (defined by NIHSS >10), and 8.2% in those with less severe strokes (NIHSS ≤ 10). Five-year dementia risk remained high, and was associated with age, previous stroke, stroke severity, dysphasia, baseline cognition, low education, white-matter disease, and diabetes. Overall, OxVasc participants with severe stroke advanced their dementia risk to that of someone 24 years older, while survivors of mild stroke brought their risk forward 4 years [2].

About half of the increased risk of dementia after stroke is in the first 6–12 months [1,2]. Overlaid with this there can be improvements in the initial months after stroke [5]. This is similar to the pattern seen with stroke-induced disability where an initial impairment improves in the months afterwards [6]. Then in the case of both dementia and disability incidence, there is a long-term change in trajectory that results in a higher likelihood of accumulating both cognitive deficits or disability for years [1,3,6]. In hemorrhagic stroke, dementia within 6 months is associated with hemorrhage size and location, while later dementia between 6 and 60 months after hemorrhage is associated with age, education, mood, and white matter disease [7]. However, these associations pertain to the absolute dementia risk—there is not a good enough understanding of the mechanisms that underlie post-stroke dementia to differentiate which participants have dementia due to the stroke alone, to a separate neurodegenerative process, or both. Alzheimer's Disease and stroke commonly co-occur, and there is conflicting evidence on whether there are additive or multiplicative effects on neurodegeneration and dementia risk [8–10].

However, we do know that the long-lasting higher risk of incident dementia after stroke is unlikely to result from vascular risk factors or silent strokes alone. Although a second clinical stroke does increase dementia risk, this occurs primarily within one year of the stroke [2], and with the exception of diabetes, vascular risk factors like hypertension and hyperlipidemia do not contribute despite their ability to increase dementia risk on their own [1,2,4]. Importantly, treatment of cardiovascular risk factors including hypertension, hyperlipidemia, and type II diabetes, either singly or in combination, have largely failed to prevent cognitive decline after stroke [11–14].

Inflammation hypothesis

Stroke has profound effects on both brain inflammation and the systemic immune system, and there is growing evidence that multifactorial immune changes may act in concert to cause dementia. Our model (Fig. 1) is that new dementia in the months after stroke is caused by a combination of stroke lesion location and size combined with a prolonged inflammatory response against the resultant lipid-rich debris. Later dementia risk then results from prolonged autoimmune responses in some stroke survivors. Finally, systemic immune changes provoked by stroke likely amplify immune responses in the brain. In the following paragraphs, we will review the accumulating evidence that inflammation can influence post-stroke cognitive outcomes.

Myelin phagocytosis and smoldering innate inflammation after CNS injury.

Following stroke, monocyte-derived macrophages infiltrate the infarct to assist microglia in the phagocytosis of cellular debris, a large fraction of which is myelin. The phagocytosis of lipid-rich myelin debris in the central nervous system (CNS) is challenging, as evidenced by the finding that crystals of cholesterol esters derived from myelin debris are present for at least 20 months in the human brain after stroke [15], and the fact that it can take several decades for myelin debris to be cleared following spinal cord injury (SCI) [16]. Myelin debris is not intrinsically pro-inflammatory [17–19]. However, it can drive smoldering inflammation and cause secondary neurodegeneration following SCI [20]. Many receptors facilitate myelin phagocytosis following CNS injury, and each has the capacity to promote pro-inflammatory cytokine production [20–22] (Fig. 2).

Stroke causes significant free radical generation and lipid peroxidation [23], and so the extent to which myelin lipids become oxidatively altered may also modify the receptor pathways through which they are cleared. Whether this is a mechanism by which the phagocytosis of myelin drives chronic inflammation and contributes to post-stroke dementia is unknown. However, Chung et al. recently compared the inflammatory response to ischemia in the brain to that in the heart, and observed that in the brain there is a prolonged immune response that takes 3–6 months to resolve, compared to 4 weeks in the heart [24]. It is characterized by an accumulation of lipid debris within foamy macrophages that coincides with the appearance of intracellular and extracellular cholesterol crystals and the induction of a second wave of pro-inflammatory cytokine and degradative enzyme production. Molecules present within chronic stroke infarcts also have access to adjacent brain tissue across permeable glial scars [25]. The seepage of neurotoxic cytokines and degradative enzymes across permeable glial scars likely contributes to the atrophy and encephalomalacia of the tissue that surrounds infarcts in the weeks and months after stroke. When the infarct is adjacent to a brain region important for cognition, this could promote post-stroke cognitive decline.

Mis-regulation of normal brain function by innate immunity

In addition to direct toxicity to neurons and infarct expansion, the inflammatory response to stroke can affect neurogenesis. Toll-like receptor 4 (TLR4) signaling in innate immune cells

following stroke enhances inflammation and exacerbates damage [26,27], potentially via decreasing the levels of neuroprotective alternative neutrophils (N2) that infiltrate the infarct following stroke [28]. In addition, TLR4 signaling also enhances neurogenesis [29]. Palma-Tortosa et al. recently demonstrated that TLR4 activation, which they propose is by ligands such as high mobility group box 1 (HMGB1) released into the cerebrospinal fluid (CSF) after stroke, drives increased proliferation of neural progenitor cells following stroke, while also promoting differentiation of type C progenitor cells into migrating neuroblasts [30]. Interestingly, Cuartero et al. recently reported that increased neurogenesis after stroke actually produces aberrant neurons that contribute to post-stroke cognitive decline in mice [31]. When neurogenesis was blocked, it prevented late cognitive decline. Thus, TLR4 may be an important target for post-stroke dementia not only due to its pro-inflammatory effects but also because of its effects on normal brain function.

Adaptive immune responses to CNS antigens

In 2015 we connected the presence of delayed dementia after stroke with immune cells in the infarct for the first time. We demonstrated that B-lymphocytes infiltrate infarcted tissue following stroke in mice, and that the ablation of B-lymphocytes 5 days post stroke using a mouse version of the drug Rituximab prevents the development of delayed cognitive deficits. We also demonstrated that a B-lymphocyte response to stroke occurs in the brains of some people with stroke and dementia [32]. Supporting that antibodies to CNS antigens are pathogenic in people, we found that antibodies to myelin basic protein after stroke are associated with cognitive decline [33], and indeed it may be that prolonged phagocytosis of myelin after stroke drives this process.

Adaptive immune responses involving both B and T lymphocytes occur after stroke, and also in SCI. With regard to T lymphocytes, T cells reactive to CNS antigens have been found in the cervical lymph nodes and spleens of mice as early as 4 days after experimental stroke [34]. Brain-derived antigens and activated T cells have been found in the lymphoid tissue of acute stroke patients [35]. Additionally, following SCI, autoantibodies are generated to GluR2/3, subunits of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptor, which when injected into the brains and spinal cords of naïve mice cause immune activation, behavioral deficits, and neuronal death [36,37]. There is evidence in both stroke and SCI that B and T-cell mediated immune responses to myelin basic protein in stroke or SCI models and human patients can influence recovery, with pro-inflammatory Th1 responses associated with more injury and worse outcomes, and tolerization to MBP improving outcomes [38–40].

B lymphocytes likely also have dual roles. Regulatory B cells that secrete IL-10 reduce infarct size and inflammation in mouse models of stroke [41,42]. Recently, Zhou et al. demonstrated that microvascular endothelial cells engulf myelin debris after spinal cord injury via an IgG opsonization dependent process, after which they promote macrophage recruitment [43]. The fact that this process is IgG dependent supports an integral role for B cells in myelin clearance following CNS injury. It is already known that antibodies promote rapid myelin clearance and effective axon regeneration after nerve injury in the peripheral nervous system (PNS) [44].

Stroke causes immunosuppression increasing the risk of post-stroke infection and subsequent immune activation

Immunosuppression is apparent within one day of stroke, persists for several weeks, and the associated increased susceptibility to bacterial infection results in a higher mortality rate [45,46]. In humans, immunosuppression is characterized by peripheral lymphopenia and reduced T-cell responsiveness [47]. In mice, it is characterized by decreased numbers of circulating and splenic B, T, and natural killer (NK) cells, and increased numbers of regulatory T cells [48,49]. The mechanism by which stroke causes immunosuppression has not been fully delineated, however, treatment of animals with the β -adrenergic receptor antagonist propranolol, or chemical ablation of the sympathetic noradrenergic terminals, prevents stroke-induced lymphocyte apoptosis, lymphopenia, and monocyte deactivation [50].

Peripheral immune influences on post-stroke dementia

However, it may be that the initial immunosuppression after stroke is actually beneficial. In the weeks following stroke, there are brain antigens released into the blood and also phagocytes in the brain become antigen-presenting cells, exit, and migrate to deep cervical lymph nodes [35]. Peripheral immunosuppression during this early period may prevent amplification of harmful auto-reactive lymphocytes. Indeed, patients that experience post stroke infections have a poorer long-term functional outcome [51], and multiple clinical studies have reported more severe neurological deficits in stroke patients presenting with a preceding infection (reviewed in [52]). We recently used mass cytometry to profile immune features after stroke in stroke survivors [53]. We found that there were distinct phases of the systemic immune response to stroke, an early innate immune response 2–3 days after stroke that is characterized by pro-inflammatory monocytes signaling with STAT3, an adaptive immune response at 5 days, and a later resolution phase still apparent at 90 days.

The strength of the early immune response at day 2 was associated with more cognitive decline between days 90 and 365 after stroke [53], which we hypothesize is due to a pro-inflammatory state acting as an adjuvant to brain antigens and promoting long-lasting adaptive immune responses. Experimental studies also show that a detrimental autoimmune response to CNS antigens is increased by systemic inflammation at the time of stroke. Animals given peripheral lipopolysaccharide show an increased tendency to develop an autoreactive TH1 response to myelin basic protein (MBP) [54]. Conversely, the induction of tolerance to MBP reduces ischemic brain damage [55]. Human studies show that autoimmune responses to brain antigens following stroke are associated with having an infection, and also with worse outcome [56]. Therefore, late post-stroke cognitive decline in some patients may be the result of early systemic infection or inflammation.

There are additional mechanisms whereby a systemic pro-inflammatory response after stroke can injure the brain. Antecedent systemic inflammation increases the trafficking and infiltration of neurotoxic immune cells from the periphery into the brain following stroke and has deleterious actions on components of the neurovascular unit, tight junctions in particular, which are essential for BBB integrity. Importantly, inhibition of neutrophil-

derived MMP-9 blocks systemic inflammation-induced exacerbation of BBB disruption and brain damage [57]. Systemic inflammation can also exacerbate CNS injury by activating microglia within the brain to produce more pro-inflammatory cytokines including IL-1, IL-6, and TNF, which exacerbate neuronal loss [58].

Therapeutic implications: How does the inflammation hypothesis bring us closer to therapies for preventing cognitive decline after stroke?

There are many knowledge gaps to fill. Repurposing already-approved drugs for autoimmune diseases may limit cognitive decline. However, we need to refine our understanding of each aspect of the immune response to stroke mentioned above. There are likely to be additional influences, for example the role of the gut-brain axis, and also inflammation certainly plays beneficial roles that will need to be disentangled from its detrimental effects. In addition, new studies and tools are needed to determine which stroke survivors already have or are going to develop chronic neuroinflammation, and if it makes them susceptible to cognitive decline.

One new approach that also may benefit stroke survivors is to enhance the processing of lipid rich myelin debris by microglia and macrophages. In March 2019, Zhou et al. demonstrated that in SCI activating adiponectin signaling with a small-molecule agonist of the adiponectin receptors 1 & 2 (AdipoRon) reduces myelin lipid accumulation within macrophages, reduces inflammation and secondary neurodegeneration, and improves recovery [59]. Significantly, this study complements an older study from the same group in 2016 that demonstrated that the intraperitoneal injection of conditioned media from embryonic stem cells every 3 days for 49 days following spinal cord injury, promotes ABCA1 mediated lipid efflux from foamy macrophages, and also improves functional recovery [60]. It will be exciting to see if AdipoRon or an equivalent strategy that enhances the processing of myelin debris following CNS injury can dampen the chronic inflammatory response to stroke and prevent post-stroke dementia.

A related approach to modulate microglia and macrophages has been investigated. Kolosowska et al. recently demonstrated that peripheral administration of IL-13 induces anti-inflammatory microglial/ macrophage responses and provides neuroprotection in ischemic stroke [61]. This study only went out as far as 14 days following stroke, and so a longer study is needed to determine the impact on cognitive trajectory.

Conclusion

Although in the past several years great strides have been made in understanding and tracking immunological and inflammatory mechanisms in post-stroke dementia there is still much to be done. Currently, the only way to prevent post-stroke dementia in patients is to reduce stroke incidence and severity. The future is bright, however. With novel methods to probe human immune responses and new mouse models of post-stroke dementia there is hope that we will be able to identify stroke survivors with chronic brain inflammation. In addition, work on improving myelin debris clearance, blocking auto-immunity, and

dampening brain inflammation is proceeding and will hopefully lead to successful treatment trials in the years ahead.

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Key points:

- The initial risk of dementia in the months after stroke is related to stroke severity, however stroke survivors have worsened cognitive trajectories for years afterwards whose causes are not well understood.
- Cell specific blood biomarkers of the acute inflammatory response to stroke measured as early as day 2 following stroke can predict long-term cognitive trajectory.
- Inflammation following stroke is 3–6 times slower to resolve compared to inflammation following ischemia in the heart, and this may be due to the high lipid content of myelin.
- Adaptive immune responses after stroke worsen cognition in a mouse model in a B lymphocyte-dependent fashion.

Figure 1. Inflammation model of post-stroke dementia.

Dementia risk after stroke is related to local neurotoxicity from prolonged phagocytosis of myelin in the infarcted tissue, and more global neurotoxicity from auto-reactive immune responses with pro-inflammatory adaptive immune cells. Systemic immune responses, which can be suppressed by stroke but elevated by subsequent infection, can promote these detrimental inflammatory effects.

Figure 2. Myelin degeneration leads to the formation of foamy macrophages that persist within chronic CNS lesions and contribute to secondary neurodegeneration in models of SCI.

The intracellular accumulation of lipid rich myelin debris, combined with intrinsic and extrinsic signals, can induce pro-inflammatory cytokine production in foamy macrophages. This contributes to chronic secondary neurodegeneration following SCI and may contribute to secondary neurodegeneration following stroke. An example of an extrinsic signal is TLR activation by DAMPs derived from myelin debris, and an example of an intrinsic signal is inflammasome activation by cholesterol crystals derived from lipid overload within phagolysosomes. ABCA1 is ATP-binding cassette transporter 1, a regulator of cholesterol efflux in foamy macrophages that is overwhelmed in models of SCI [62]. Receptors that bind myelin: CR3, Complement receptor 3; FcR, Fc gamma receptor; Mac-2, MAC-2/ Galectin-3 receptor; SRAI/II, Scavenger receptor AI/II; MARCO, Macrophage receptor with a collagenous structure; LRP1, low density lipoprotein receptor-related protein 1; TREM2, Triggering receptor expressed on myeloid cells 2.