European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2023 vol. 12, ISSUE N. 2, May-August

THE AFTERMATH OF ISCHEMIC STROKE: INFLAMMATION, COMORBIDITY, AND DISABILITY

R. Ghadirpour[1,2*]

[1] Neurosurgery-Neurotraumatology Unit, University Hospital of Parma, Parma, Italy;
[2] Emergency Neurosurgery Unit, IRCCS "Arcispedale Santa Maria Nuova" of Reggio Emilia, Reggio Emilia, Italy.

Correspondence to:
Reza Ghadirpour,
Neurosurgery-Neurotraumatology Unit,
University Hospital of Parma,
Viale Gramsci 14,
43100 Parma, Italy.
e-mail: Reza.Ghadirpour@ausl.re.it

ABSTRACT

Globally, stroke is the second leading cause of mortality and disability, and the incidence is predicted to rise in the future with the increasing ageing population and a number of young-onset cases. Of the two types of stroke, hemorrhagic and ischemic, ischemic stroke is the most common form and accounts for approximately 87% of cases. It results from the disruption of blood flow to the brain, which occurs with the obstruction of blood vessels; the loss of blood circulation results in the loss of nutrients and oxygen reaching the brain, which leads to the death of neurons and the loss of neurologic function. The characteristics of ischemic stroke include neurologic and systemic inflammation, comorbidity, and severe disability. The initial injury in a stroke can lead to death, and survivors are often left with severe disabilities such as hemiplegia, paralysis or weakness that affects one side of the body. Coexisting medical conditions, such as diabetes mellitus and cardiovascular disease, are essential to stroke. They are usually the cause of the stroke itself, and the severity and type can is associated with long-term outcomes and mortality. Here, we examine these dimensions in ischemic stroke and the ways in which they ultimately predict patient outcomes.

KEYWORDS: *stroke, ischemia, inflammation, comorbidity, disability*

INTRODUCTION

Stroke is the second leading cause of disability and mortality worldwide, with 13.7 million strokes reported globally in 2016 (1, 2), and ischemic stroke accounting for approximately 87% of these (3). The incidence of stroke is expected to increase drastically due to the ageing population and rising number of young people affected in lower and middle-income nations (1).

Ischemic stroke results from the obstruction of blood vessels which supply the brain with blood; the loss of blood circulation prevents oxygen and nutrients from reaching the brain, resulting in the death of neuronal cells and the loss of neurologic function. Stroke can occur from the blockage of arterial circulation, an ischemic stroke, or a burst blood vessel in the brain, a hemorrhagic stroke. Between these two main forms, ischemic stroke is the most common type and a leading neurovascular cause of death and disability (4). Atherosclerosis is the primary cause of ischemia and can cause cerebral thrombosis or embolism.

Received: 11 May, 2023
Accepted: 31 May, 2023

2974-6345 (2023)
Copyright © by BIOLIFE
This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder. Unauthorized reproduction may result in financial and other penalties. Disclosure: all authors report no conflicts of interest relevant to this article.

Brain ischemia is characterized by neurologic and systemic inflammation, comorbidity, and severe disability. In this paper, we highlight the role of inflammation in ischemic stroke, the related sequela that accompanies and leads to stroke, and the debilitating aftereffects.

Post-stroke inflammation

The loss of blood circulation to the brain that results from ischemic stroke induces a complex chain of biochemical and molecular events, the ischemic cascade, that causes a local neuroinflammatory response and affects systemic immunity (5). There are three general phases of immune response that affect systemic immunity after stroke.

Immediately following the onset of stroke, the peripheral immune system responds to brain injury, which is then followed by a state of immunosuppression with loss of immune cells and responsiveness, increasing susceptibility to stroke-associated infections such as pneumonia (6). Finally, a chronic third phase of sustained low-grade inflammation occurs in the aftermath of a stroke, which is believed to impact the severity of patient outcomes (5).

The initial ischemic injury may produce necrosis of brain cells, while the following ischemic cascade results in further cerebral injury over the course of progressing hours and days (7). Innate immune cells circulating in the brain are engaged at the start of the stroke, followed by the invasion of blood-borne immune cells and the activation of immune cells such as microglia and mast cells residing in the brain (8). Intravascular inflammatory events activate the complement system, which adds to cerebral damage.

Neutrophils are recruited immediately and release metalloproteases (MMP9), elastase, cathepsin G, reactive oxygen and nitrogen species, and the pro-inflammatory cytokine interleukin (IL)-1 (9,10), which mediate inflammation. Peripheral immune cells may enter the brain through the blood-brain barrier (BBB), which opens within hours following ischemic stroke; the choroid plexus and monocytes and neutrophils may also enter through skull-meninges connections such as the leptomeningeal vessels (11,12).

Microglia engage in phagocytosis but are initially activated before the death of neurons, and it appears that microglia involvement has a beneficial effect on limiting post-stroke inflammation (13). On the other hand, microglia activation leads to the release of inflammatory cytokines, which participate in brain damage. Damage-associated molecular patterns (DAMPS) and cytokines generated in the brain in the initial phase of ischemic injury can infiltrate circulation, activating systemic immunity and triggering inflammation (14).

Post-stroke, systemic inflammation can cause acute and chronic complications for patients. With stroke, there is an acute systemic inflammatory reaction and a longer-term low-grade inflammatory response; the combination of these two reactions has been associated with decreased functional outcomes and higher mortality rates in stroke survivors (15). Plasma levels of different inflammatory markers, including the cytokines IL-1, IL-6, and C-reactive protein, have been seen to be elevated in stroke patients (16), and can predict stroke recurrence and functional outcome (17). IL-6 binds to its IL-6 receptors on brain endothelial cells, leading to the increased release of prostaglandin E2 (PGE2), which stimulates the hypothalamus, causing body temperature to rise and producing fever and mediating inflammation (18) (Fig.1).

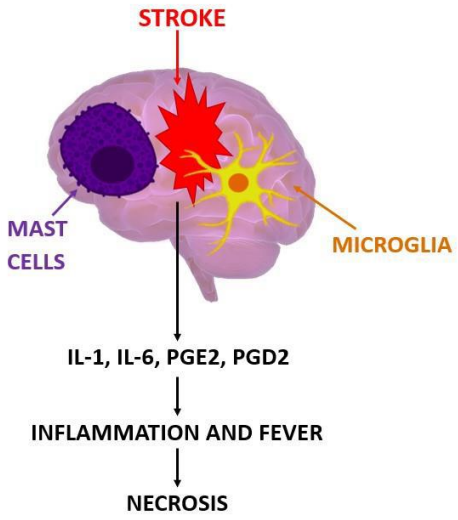

Fig. 1. *Impact of stroke on the brain. Stroke affects brain cells, including microglia and mast cells which secrete inflammatory cytokines after activation, such as IL-1 and IL-6, as well as prostaglandins (PGE2 and PGD2, respectively).*

Much research has begun to focus on the immunological mechanisms underlying stroke, hoping that the modulation of neuroinflammatory pathways could have therapeutic implications (8).

Comorbidity

Comorbidities are a central element of ischemic stroke and are usually the cause of stroke in adults. These comorbidities can be preexisting or post-stroke acquired, with the most frequent being cardiovascular diseases and diabetes mellitus. In fact, the incidence of stroke occurring in the absence of other medical conditions is very low, having been suggested to occur in less than 6% of cases (19,20). Coexisting medical disorders also have great effects on post-stroke outcomes for patients, as they may affect the patient's participation in rehabilitation as well as the efficacy of such treatment.

Medical complications following stroke are common, reported in 40%-96% of patients, and are associated with poor outcomes (21-23) and negative implications for rehabilitation. In one study, stroke severity, atrial fibrillation, and the comorbidity of coronary artery disease and diabetes were associated with disadvantageous outcomes (24). Another study showed a negative correlation between functional outcomes at discharge and mortality rates and the severity and number of coexisting medical conditions in post-stroke patients (25). Frequent comorbid conditions in stroke include hypertension, hypertensive cardiovascular disease, coronary heart disease, diabetes mellitus, obesity, tumor, arthritis, and cardiovascular diseases (24,26). Cardiovascular diseases frequently occur as comorbidity and were seen to affect 40% of post-stroke patients during inpatient rehabilitation (27). However, some stroke-related comorbidities can be modifiable such as atherosclerosis, diabetes mellitus, infections, and certain cardiovascular diseases. For example, hypertension is the most prevalent comorbidity for stroke patients and is a modifiable risk factor.

Furthermore, the inflammatory response occurring after ischemic stroke causes immunodepression associated with post-stroke infections (6). Combined with coexisting medical disorders, modifiable and non-modifiable risk factors influence the mortality rates of stroke patients (28).

Post-stroke disability

Stroke is a leading cause of death, and survival is often accompanied by severe chronic disabilities (29). Additionally, functional deficits following stroke are associated with readmission in hospital, mortality, and early death (30). Disability following ischemic stroke affects between 24%-54% of survivors (31). The burden of disability is more drastic in low and middle-income nations, where regional medical services and rehabilitative care may be lacking, and environmental factors may increase the incidence and severity of post-stroke disability (32).

The location and severity of brain damage predicts the long-term effects produced after stroke, and other factors that influence disability include age of patient at stroke onset, neurological and cognitive deficits, depression, and social support (32). About 70-80% of patients who survive stroke will have disabilities that require rehabilitation and long-term care (33). Data from an Australian study has shown that just over one-third of stroke survivors suffered from a disability that affected their daily functioning, and that of these, 12% needed residential care (34).

Disabilities vary, but frequently there can be changes in speech, learning, and cognition, and hemiplegia, paralysis or weakness that affects one side of the body. Furthermore, stroke may also produce permanent loss of function. Hemiplegia produces diverse complications with motor, cognitive, perceptive, and sensory abnormalities, in addition to visual and language complications (35). The rate of upper-limb disorders is very high post-stroke, with 85% of patients affected in the acute stage, with the frequency dropping to 55-75% after 3 to 6 months from stroke (36,37). Patients often have a deterioration in motor skills that can affect grip strength, causing problems with holding onto objects and the ability to perform a variety of tasks (38). This impairment can greatly reduce patients' self-care and socialization abilities.

Permanent disability interferes with the everyday functioning of patients, affecting their ability to care for themselves and participate in social activities, which ultimately leads to a significantly reduced health-related quality of life (39,40). Post-stroke depression is another prevalent disorder affecting survivors, with studies showing a prevalence rate in between 18%-61% of post-stroke patients (41,42). Depression after stroke has also been related to functional disability, affecting cognition, balance, walking ability, and patient independence (43,44).

Early treatment and rehabilitation are vital to reduce the impact of disability and can improve recovery and patient outcomes and reduce overall healthcare needs.

CONCLUSIONS

Cerebral stroke is a leading cause of death and disability in the modern world, and the incidence is expected to rise drastically over the next decades. Three key features characterize ischemic stroke: neurologic and systemic inflammation, comorbidity, and disability.

Ischemic stroke occurs when there is a disruption in blood circulation in the brain, which results in brain damage with severe consequences. In stroke, the interruption of blood circulation can lead to death or the loss of neurologic function, and survivors are often left with serious chronic disabilities that affect daily functioning and quality of life. These disabilities can include changes in speech, learning, and cognition, and hemiplegia. After the initial ischemic injury, an inflammatory cascade proceeds that results in neuroinflammation and affects systemic immunity. These inflammatory events create a higher rate of susceptibility to stroke-associated infections and may ultimately impact the severity of patient outcome.

Another characterizing feature of ischemic stroke is comorbidity, which is often the initial cause of stroke and an aggravating factor in rehabilitation and recovery. Furthermore, the severity and number of coexisting medical conditions in post-stroke patients have been associated with long-term outcomes and mortality rates. Comorbidities vary, with cardiovascular disease and diabetes mellitus being the most prominent and frequent.

Stroke is responsible for a high level of mortality and produces debilitating consequences in its aftermath. Recently, the immunological mechanisms underlying stroke have emerged as a course of study with the hope that they could be of therapeutic value. Further research is necessary to provide further insight into the mechanisms of stroke and to develop new treatments.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Katan M, Luft A. Global Burden of Stroke. *Seminars in Neurology*. 2018;38(02):208-211. doi:https://doi.org/10.1055/s-0038-1649503
2. Feigin VL, Abajobir AA, Abate KH, et al. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet Neurology*. 2017;16(11):877-897. doi:https://doi.org/10.1016/s1474-4422(17)30299-5
3. Saini V, Guada L, Yavagal DR. Global Epidemiology of Stroke and Access to Acute Ischemic Stroke Interventions. *Neurology*. 2021;97(20 Supplement 2):S6-S16. doi:https://doi.org/10.1212/WNL.0000000000012781
4. Fan J, li X, yu X, et al. Global Burden, Risk Factors Analysis, and Prediction Study of Ischemic Stroke, 1990–2030. *Neurology*. 2023;101(2):e137-e150. doi:https://doi.org/10.1212/wnl.0000000000207387
5. Simats A, Liesz A. Systemic inflammation after stroke: implications for post-stroke comorbidities. *EMBO Molecular Medicine*. 2022;14(9). doi:https://doi.org/10.15252/emmm.202216269
6. Faura J, Bustamante A, Miró-Mur F, Montaner J. Stroke-induced immunosuppression: implications for the prevention and prediction of post-stroke infections. *Journal of neuroinflammation*. 2021;18(1):127. doi:https://doi.org/10.1186/s12974-021-02177-0
7. Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. *Trends in Neurosciences*. 1999;22(9):391-397. doi:https://doi.org/10.1016/s0166-2236(99)01401-0
8. Iadecola C, Buckwalter MS, Anrather J. Immune responses to stroke: mechanisms, modulation, and therapeutic potential. *Journal of Clinical Investigation*. 2020;130(6):2777-2788. doi:https://doi.org/10.1172/jci135530
9. Allen C, Thornton P, Denes A, et al. Neutrophil Cerebrovascular Transmigration Triggers Rapid Neurotoxicity through Release of Proteases Associated with Decondensed DNA. *The Journal of Immunology*. 2012;189(1):381-392. doi:https://doi.org/10.4049/jimmunol.1200409
10. Stowe AM, Adair-Kirk TL, Gonzales ER, et al. Neutrophil elastase and neurovascular injury following focal stroke and reperfusion. *Neurobiology of Disease*. 2009;35(1):82-90. doi:https://doi.org/10.1016/j.nbd.2009.04.006

11. Otxoa-de-Amezaga A, Gallizioli M, Pedragosa J, et al. Location of Neutrophils in Different Compartments of the Damaged Mouse Brain After Severe Ischemia/Reperfusion. *Stroke*. 2019;50(6):1548-1557. doi:https://doi.org/10.1161/strokeaha.118.023837
12. Cai R, Pan C, Alireza Ghasemigharagoz, et al. Panoptic imaging of transparent mice reveals whole-body neuronal projections and skull–meninges connections. *Nature Neuroscience*. 2019;22(2):317-327. doi:https://doi.org/10.1038/s41593-018-0301-3
13. Lalancette-Hebert M, Gowing G, Simard A, Weng YC, Kriz J. Selective Ablation of Proliferating Microglial Cells Exacerbates Ischemic Injury in the Brain. *Journal of Neuroscience*. 2007;27(10):2596-2605. doi:https://doi.org/10.1523/jneurosci.5360-06.2007
14. Bower NI, Hogan BM. Brain drains: new insights into brain clearance pathways from lymphatic biology. *Journal of Molecular Medicine (Berlin, Germany)*. 2018;96(5):383-390. doi:https://doi.org/10.1007/s00109-018-1634-9
15. Dziedzic T. Systemic inflammation as a therapeutic target in acute ischemic stroke. *Expert Review of Neurotherapeutics*. 2015;15(5):523-531. doi:https://doi.org/10.1586/14737175.2015.1035712
16. Lambertsen KL, Biber K, Finsen B. Inflammatory Cytokines in Experimental and Human Stroke. *Journal of Cerebral Blood Flow & Metabolism*. 2012;32(9):1677-1698. doi:https://doi.org/10.1038/jcbfm.2012.88
17. Aref HMA, Fahmy NA, Khalil SH, Ahmed MF, ElSadek A, Abdulghani MO. Role of interleukin-6 in ischemic stroke outcome. *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery*. 2020;56(1). doi:https://doi.org/10.1186/s41983-019-0121-8
18. Eskilsson A, Mirrasekhian E, Dufour S, Schwaninger M, Engblom D, Blomqvist A. Immune-Induced Fever Is Mediated by IL-6 Receptors on Brain Endothelial Cells Coupled to STAT3-Dependent Induction of Brain Endothelial Prostaglandin Synthesis. *Journal of Neuroscience*. 2014;34(48):15957-15961. doi:https://doi.org/10.1523/jneurosci.3520-14.2014
19. Nelson MLA, McKellar KA, Yi J, et al. Stroke rehabilitation evidence and comorbidity: a systematic scoping review of randomized controlled trials. *Topics in Stroke Rehabilitation*. 2017;24(5):374-380. doi:https://doi.org/10.1080/10749357.2017.1282412
20. Gallacher KI, Batty GD, McLean G, et al. Stroke, multimorbidity and polypharmacy in a nationally representative sample of 1,424,378 patients in Scotland: implications for treatment burden. *BMC Medicine*. 2014;12(1). doi:https://doi.org/10.1186/s12916-014-0151-0
21. Johnston KC, Li JY, Lyden PD, et al. Medical and neurological complications of ischemic stroke: experience from the RANTTAS trial. RANTTAS Investigators. *Stroke*. 1998;29(2):447-453. doi:https://doi.org/10.1161/01.str.29.2.447
22. Langhorne P, Stott DJ, Robertson L, et al. Medical Complications After Stroke. *Stroke*. 2000;31(6):1223-1229. doi:https://doi.org/10.1161/01.str.31.6.1223
23. Karatepe A, Gunaydin R, Kaya T, Turkmen G. Comorbidity in patients after stroke: Impact on functional outcome. *Journal of Rehabilitation Medicine*. 2008;40(10):831-835. doi:https://doi.org/10.2340/16501977-0269
24. Fischer U, Arnold M, Nedeltchev K, et al. Impact of comorbidity on ischemic stroke outcome. *Acta Neurologica Scandinavica*. 2006;113(2):108-113. doi:https://doi.org/10.1111/j.1600-0404.2005.00551.x
25. Goldstein LB, Samsa GP, Matchar DB, Horner RD. Charlson Index Comorbidity Adjustment for Ischemic Stroke Outcome Studies. *Stroke*. 2004;35(8):1941-1945. doi:https://doi.org/10.1161/01.str.0000135225.80898.1c
26. Gresham GE, Phillips TF, Wolf PA, McNamara PM, Kannel WB, Dawber TR. Epidemiologic profile of long-term stroke disability: the Framingham study. *Archives of physical medicine and rehabilitation*. 1979;60(11):487-491.
27. Black-Schaffer RM, Kirsteins A, Harvey RJ. 2. Comorbidities and complications. *Archives of Physical Medicine and Rehabilitation*. 1999;80(5 Suppl 1). doi:https://doi.org/10.1016/s0003-9993(99)90096-5
28. De Stefano F, Mayo T, Covarrubias C, Fiani B, Musch B. Effect of comorbidities on ischemic stroke mortality: An analysis of the National Inpatient Sample (NIS) Database. *Surgical Neurology International*. 2021;12:268. doi:https://doi.org/10.25259/sni_415_2021
29. Krishnamurthi Rita V, Ikeda T, Feigin Valery L. Global, Regional and Country-Specific Burden of Ischaemic Stroke, Intracerebral Haemorrhage and Subarachnoid Haemorrhage: A Systematic Analysis of the Global Burden of Disease Study 2017. *Neuroepidemiology*. 2020;54(2):1-9. doi:https://doi.org/10.1159/000506396
30. Gaynor E, Rohde D, Large M, et al. Cognitive Impairment, Vulnerability, and Mortality Post Ischemic Stroke: A Five-Year Follow-Up of the Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S) Cohort. *Journal of Stroke and Cerebrovascular Diseases*. 2018;27(9):2466-2473. doi:https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.05.002

31. Sacco RL. Risk factors, outcomes, and stroke subtypes for ischemic stroke. *Neurology*. 1997;49(Issue 5, Supplement 4):S39-S44. doi:https://doi.org/10.1212/wnl.49.5_suppl_4.s39
32. Lv Y, Sun Q, Li J, Zhang W, He Y, Zhou Y. Disability Status and Its Influencing Factors Among Stroke Patients in Northeast China: A 3-Year Follow-Up Study. *Neuropsychiatric Disease and Treatment*. 2021;Volume 17:2567-2573. doi:https://doi.org/10.2147/ndt.s320785
33. Nichols-Larsen DS, Clark PC, Zeringue A, Greenspan A, Blanton S. Factors Influencing Stroke Survivors' Quality of Life During Subacute Recovery. *Stroke*. 2005;36(7):1480-1484. doi:https://doi.org/10.1161/01.str.0000170706.13595.4f
34. Australian Institute of Health and Welfare (AIWI). *Stroke and its management in Australia: an update*. Canberra, ACT, Australia: AIHW, 2013.
35. Kim K, Cha YJ. Cane Length Influence on the Plantar Pressure Distribution of Adult Hemiplegia Patients. *Journal of Physical Therapy Science*. 2011;23(3):451-454. doi:https://doi.org/10.1589/jpts.23.451
36. Ryerson SD. *Hemiplegia in neurological rehabilitation, Umphred DA (ed), 4th ed*. St. Louis: Mosby, 2001, pp 741–789.
37. Olsen TS. Arm and leg paresis as outcome predictors in stroke rehabilitation. *Stroke*. 1990;21(2):247-251. doi:https://doi.org/10.1161/01.str.21.2.247
38. Baak B, Bock O, Dovern A, Saliger J, Karbe H, Weiss PH. Deficits of reach-to-grasp coordination following stroke: Comparison of instructed and natural movements. *Neuropsychologia*. 2015;77:1-9. doi:https://doi.org/10.1016/j.neuropsychologia.2015.07.018
39. Tsalta-Mladenov M, Andonova S. Health-related quality of life after ischemic stroke: impact of sociodemographic and clinical factors. *Neurological Research*. 2021;43(7):553-561. doi:https://doi.org/10.1080/01616412.2021.1893563
40. Zhou X, Du M, Weng Y, Zhou L. Hard return: the development and transformation process of social participation in stroke survivors; a qualitative study and initial theory. *Clinical Rehabilitation*. 2020;34(6):824-836. doi:https://doi.org/10.1177/0269215520917191
41. House A, Dennis M, Mogridge L, Warlow C, Hawton K, Jones L. Mood Disorders in the Year after First Stroke. *British Journal of Psychiatry*. 1991;158(1):83-92. doi:https://doi.org/10.1192/bjp.158.1.83
42. Kong KH, Yang SY. Health-related quality of life among chronic stroke survivors attending a rehabilitation clinic. *Singapore medical journal*. 2006;47:213–8.
43. Paolucci St, Gandolfo C, Provinciali L, Torta R, Toso V. The Italian multicenter observational study on post–stroke depression (DESTRO). *Journal of Neurology*. 2006;253(5):556-562. doi:https://doi.org/10.1007/s00415-006-0058-6
44. Srivastava A, Taly A, Gupta A, Murali T. Post-stroke depression: Prevalence and relationship with disability in chronic stroke survivors. *Annals of Indian Academy of Neurology*. 2010;13(2):123. doi:https://doi.org/10.4103/0972-2327.64643