Avens Publishing Group
J Ocular Biol
August 2024 Volume 8 Issue 1

Open Access Review Article

Journal of Ocular Biology

The Association of Ocular Disease in the Development of Cerebrovascular Accidents

Chevy Singh[1]* and Ting Wang[2]

[1]*Indiana University School of Medicine, Indianapolis, Indiana, USA*
[2]*Eugene & Marilyn Glick Eye Institute, Indianapolis, Indiana, USA*

***Address for Correspondence:** Chevy Singh, Indiana University School of Medicine, Indianapolis, Indiana USA. Email Id: singshiv@iu.edu

Submission: 30-July-2024
Accepted: 20-August-2024
Published: 24-August-2024

Keywords

Cerebrovascular Accident; Stroke; Diabetic Retinopathy; Cataract, Glaucoma; Open-Angle Glaucoma

Abstract

Purpose: Cerebrovascular Accident or "stroke" is a leading cause of death with very limited treatments available. To reduce the incidence, current efforts are focused on identifying and mitigating the risk factors leading to stroke. In this study, we review common ocular pathologies such as cataracts, glaucoma, and diabetic retinopathy and their association with stroke.

Methods: A review of literature regarding ocular pathology in the development of stroke was performed.

Results: The mechanisms behind the development of cataracts, diabetic retinopathy, and glaucoma along with current literature studying the effect of these ocular diseases on the incidence of stroke were discussed.

Conclusions: Studies suggest a correlation between ocular disease and stroke may exist. In some cases, such as diabetic retinopathy, the stage of the disease can be used to assessthe level of risk. However, further research is needed due to conflicting results.

Introduction

Cerebrovascular Accident, or more commonly referred to as "stroke," is the second leading cause of death and the third leading cause of disability worldwide [1]. There are two main types of strokes, haemorrhagic and ischemic, with the latter being more predominant [1,2]. The World Stroke Organization notes over 100 million people in the world have experienced a stroke and 1 in 4 adults over the age of 25 will have a stroke in their lifetime [2]. Despite increasing awareness of stroke, the number of cases continues to rise over time [2].

The deficits seen with a stroke are often correlated to the inflicted areas of the brain and/or brainstem[3]. Commonly associated symptoms of a stroke include unilateral weakness, numbness, difficulty speaking, and understanding speech [3]. Current management of stroke is very limited. Ischemic strokes can be treated with alteplase or tenecteplase if estimated last time of normal function was within 4.5 hours [4,5]. Although some level of recovery does occur in the hospital setting after an acute event, recovery of function can occur over the next couple of years [6,7]. Unfortunately, only 10-20% of stroke patients experience a full recovery [6,7]. Due to the limited treatment options, prevention is key in managing stroke [1,2]. Determining the risk factors that predispose individuals to stroke is crucial as early intervention can significantly improve overall survival rates [1,2].

Much like stroke, common ocular diseases such as cataracts, diabetic retinopathy (DR), glaucoma, and age-related macular degeneration (AMD) are becoming increasingly prevalent [8-11]. Although many of these afflictions share overlapping risk factors to stroke, some studies link these diseases to further increasing the risk of stroke [12-15]. The aim of this study is to review the major findings linking stroke with predominant ocular diseases. Understanding this connection could ultimately transform patient care, leading to a reduced incidence of stroke.

Diabetic Retinopathy

DR is seen in about 34.6% of patients with diabetes mellitus (DM), making it one of the most common microvascular manifestations of this systemic disease [16]. Several studies, including the ACCORD study, link glycemic index with stage progression of DR [17-19]. With the increasing number of diabetics each year, DR is among the leading causes of vision loss in the world [16,20]. DM is also a proposed risk factor in the development of stroke [21,22]. High levels of blood glucose can lead to increased clot deposits within blood vessels, narrowing or completely blocking flow to crucial structures in the head and neck [21,22]. This excess blood sugar can also negatively impact the structural integrity of these vessels, reducing elasticity and narrowing blood flow [21,22]. The vessels supplying the retina undergo a similar change in response to hyperglycemia and give rise to DR [23]. Due to similar mechanisms, studies examined for a potential link between stroke and DR. Several studies have shown DR as a predictor of stroke, although this was not a uniform finding [14,24-29].

In a large study looking at this association by Hankey et al., 9795 patients aged 50-75 with type 2 DM were followed for 5 years to determine the risk of stroke, type of stroke, and independent factors associated withfurther increasing the rate of stroke [28]. Their results showed 6.7 strokes per 1000 patients, 82% ischemic strokes of which 36% originated from small vessels, 17% large vessels, and 13% embolic from the heart [28]. Of the independent risk factors, DR was significantly associated with small vessel ischemic stroke when compared to the overall DM cohort [28]. This suggests stroke from DR may be associated with different mechanisms than patients without DR. As DR affects the small vessel of the eye, the presence of this disease may be predictive of future small vessel-associated stroke.

The incidence of stroke in patients of type 1 DM was lower than seen with type 2 DM, with a rate of 3.0 per 1000 patients over a 15-year follow-up period in similarly aged groups [28]. Hägg et

ISSN: 2334-2838

al. studied 4,083 patients with type 1 DM on the development of stroke along with the impact of diabetic nephropathy and severe diabetic retinopathy (SDR) on this risk [29]. Authors found SDR to be independently associated with a higher risk of developing stroke [29]. These results are not uniform as other studies examining this relationship found type 1 DM SDR to be associated with increased cardiovascular and peripheral artery disease, but not stroke when compared to type 1 DM without DR [30].A recent systemic review performed by Wang et al. including 19 studies with 45,495 patients studied the association between DR and risk of stroke [14]. In 13 studies looking at DR derived from type 2 DM, DR was associated with a significantly increased risk of stroke when compared to those with diabetes without DR. Additionally, authors found a trend between increasing severity of DR and increased stroke risk [14]. Interestingly, no association was noted observing four studies studying DR developed from type 1 DM and stroke [14]. Due to the low sample size and differing criteria, current results studying this relationship are inconclusive.

Recent studies show compelling evidence indicating the presence of DR associated with type 2 DM independently further elevates the risk of stroke compared to patients with DM without DR. This is believed to be caused by an increase of small vessel changes seen in this population when compared to DM without DR [28]. This same conclusion cannot be said about type 1 DM patients. Although some of the current studies adjust for metabolic disease, type 1 DM patients present with different comorbidities than its lifestyle-associated counterpart [31]. Additionally, correcting for medical interventions such as the use of insulin was not well defined in these studies. As type 1 DM is typically diagnosed and treated earlier than type 2, these patients may have a lower or delayed risk of stroke. With DR stage correlating to stroke risk, ocular exams can be done to monitor the progress of DR as well as stroke.

Glaucoma

Glaucoma is a group of eye conditions where irreversible damage occurs to the optic nerve in the back of the eye [32, 33]. Open-angle glaucoma (OAG) is the most common form, making up more than 80% of all diagnoses, and is caused by improper drainage of the nutritious aqueous humor of the eye through currently unclear mechanisms [32, 33]. This build-up of fluid in the anterior chamber of the eye increases the intraocular pressure and compresses the nearby optic nerve. This stress to the optic nerve characteristically presents with a gradual loss of peripheral vision [33]. In addition to eye pressure, other proposed modifiable risk factors include the use of corticosteroids, diabetes, hypertension, and a smoking history [34]. The association between stroke and glaucoma is not widely known.

In a study by Ho et al. 4,032 patients with OAG were compared to an age, gender, geographic location, and comorbid condition matched control group to examine if OAG is associated with an increased incidence of stroke [15]. Analysis at the 5-year follow-up showed that 14.9% of the patients in the OAG group and 9.5% in the control cohort developed a stroke, a 1.52-fold increase. The patients with OAG also demonstrated a significantly lower free survival rate than the comparison group [15]. This finding was also supported genetically by a recent gene-wide association study (GWAS) looking at single nucleotide polymorphisms (SNPs) related to glaucoma and datasets for ischemic stroke from the MEGASTROKE consortium [35]. Glaucoma was found to be significantly associated with an increased risk of ischemic stroke, poor prognosis after stroke, and functional outcome after stroke [35, 36]. Not many studies have found stroke to increase the risk of glaucoma in the future [35].

Most of the current studies focus solely on OAG and the type of stroke was not differentiated. To determine if the same trend is noted across other types of glaucoma or stroke, further analysis is warranted. Other potential confounding variables such as alcohol consumption, cardiovascular disease, and family history of glaucoma or stroke were not uniformly adjusted across all studies [34]. Future studies should investigate the severity of glaucoma with the development of stroke. An increased risk associated with a more advanced stage of glaucoma could further strengthen this correlation. Current management of patients with glaucoma does not include a stroke risk assessment. The studies presented here suggest the development of stroke may be related to a history of glaucoma and having these patients examined and treated for vascular risk factors can lower the overall incidence of stroke.

AMD

AMD is the degeneration of the macula, responsible for providing central vision [37]. It is the leading cause of vision loss in patients over the age of 65 and the rate of cases continues to grow [37]. Symptoms of AMD include blurriness of central vision, difficulty seeing in low light settings, and distortion of straight lines [37, 38]. These symptoms can worsen over time, with no current cure available. AMD can be broken down into two types: the more common dry AMD and the more aggressive wet AMD [37, 38]. Dry AMD is notable for the presence of drusen, pigment abnormalities, and geographic abnormalities, whereas wet AMD is characterizedby abnormal blood vessel growth under the retina [37,38]. AMD can be further divided into early or late stages, with the early stage being asymptomatic [39]. Due to the severity of symptoms, the presence of neovascularization in wet AMD classifies it as a latestage. The exact cause of AMD remains unclear with proposed risk factors of age greater than 50, obesity, hypertension, diets high in saturated goods, and family history of AMD [39, 40]. There has been conflicting evidence between the association of AMD and stroke [13, 41-44].

Wong et al. compared 498 patients with early-stage AMD to 10,405 control persons between ages 49 to 73 without a history of stroke or coronary heart disease over a 10-year period [42]. Authors found that early-stage AMD was associated with a higher cumulative and adjusted risk of stroke compared to control. This finding did not substantially change after adjusting for additional cofounders such as systolic blood pressure, cigarette smoking, diabetes, and the use of anti-hypertensive medications. However, a meta-analysis studying this association was done in 2015, incorporating 9 studies with patients with and without early-stage AMD (N = 1,420,978) [13]. The authors found no significant association between early AMD and the incidence of stroke.

Tan et al. noted an association using late-stage AMD patients of a similar age range, noting a 5-fold higher risk of cardiovascular mortality and 10-fold higher stroke mortality [43]. Interestingly, in studieswhere neovascular AMD was evaluated, those aged 65 years

ISSN: 2334-2838

old and older were associated with a higher risk of stroke [41,44]. Other studies looking at patients < 65 years of age with neovascular AMD and incidence of stroke did not reach significance when compared to the control cohort [41,44].

Additional studies are needed to further evaluate AMD as a possible risk factor for stroke. Factors such as dietary deficiencies, use of AREDS 2 vitamins, excessive light exposure, or delineation of aggressive reticular macular disease were not considered in current studies [13,40]. Data regarding late-stage AMD has shown mixed results. Non-significance may be related to studies not adjusting for patients receiving intravitreal antiangiogenic therapy for neovascular AMD. Studies onstroke in cases of late-stage AMD suggest that older age is a significant risk factor. Age-related collagen changes, lipid deposition, and narrowing of choriocapillaris are possible mechanisms in the development of AMD as well as stroke [1,45]. Given conflicting results, AMD may be an associated factor, along with age, in the future development of stroke.

Cataracts

Cataract is the leading cause of blindness in the world and is associated with poor quality of life and shortened life expectancy [46,47]. Through changes in the proteins, pigmentation, and fibrous proliferation, the crystalline lens that focuses light onto the retina is obscured [46]. There are many forms of cataracts, the most common being age-related with a multifactorial pathogenesis that is currently unclear. By age 65, most of the United States population will develop cataracts [48]. By means of cataract surgery, this common ophthalmologic condition is largely correctable [46,47]. The correlation between CVA and cataract is not clear. Although both processes have similar risk factors such as increasing age, diabetes, smoking, and obesity; it is debated whether the presence of cataracts increases the risk of stroke or vice versa [1,46].

A study by Huang et al. investigated early onset cataract (EOC)in 1,293 patients and compared it to a propensity score-matched cohort of 5,172 individuals to assess the risk of developing ischemic stroke [12]. EOC was defined by a new diagnosis of cataract between the ages of 20 to 55. Comorbidities such as hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, obesity, heart failure, chronic kidney disease, asthma, heart failure, and obesity were non-significant between the groups. After a mean follow-up of approximately 5.3 years, the EOC group demonstrated a non-significant 1.48-fold higher risk of developing ischemic stroke than the comparison cohort [12]. Interestingly, subgroup analysis of females showed the EOC group had a significant 1.97-fold higher risk of ischemic stroke. This was not seen in the subgroup analysis of the male patients.

Studies have also noted stroke in the development of cataracts. Chen et al. compared 5,462 patients with a history of acute stroke without severe disability to an age- and sex-matched control of 25,434 patients in need of cataract surgery [47]. Examining patients after a 5-year follow-up, 8.8% of stroke patients and 7.2% of controls received cataract surgery. This 30% increase in the incidence of cataract surgery from patients with a history of stroke was statistically significant compared to control [47]. In addition, recent large studies suggest that those who underwent cataract surgery showed significantly higher mortality rates for events related to vascular, cancer, accident, Alzheimer's disease, respiratory disease, and renal disease [49].

Given the diverse findings in research on the link between these two diseases, further investigation into this association is needed. It is unclear if the same association with stroke is seen with cataract formed due to alternate causes such as radiation exposure, trauma, high myopia, uveitis, or a drug reaction. As the existing research supports a bidirectional correlation, further investigation of the mechanism of cataract formation and cataract surgery is needed. On the other hand, due to their similar inciting factors, the relationship between cataract and stroke may be of co-morbid conditions stemming from another underlying disease process. A history of cataracts or cataract surgery may indicate an increased risk of future stroke or be associated with a past stroke.

Conclusion

The current treatment for stroke is very limited, making prevention the best therapy. What is not commonly known is the association of ocular disease with future development of stroke. This study is unique because it is the only study, to our knowledge, to summarize several common ocular pathologies and discuss them as risk factors for stroke. These findings can serve in the earlier recognition of high-risk individuals and aid in prevention. Currently, about 45% of the adult population in the United States does not get annual comprehensive eye exams, with several million Americans having undiagnosed or inadequately treated visual impairments [50]. Results from this study suggest practitioners should obtain an ocular history from patients while also endorsing yearly eye examinations. Those with signs of early cataracts, DR, OAG, or AMD should be recommended lifestyle modifications. This would not only preserve vision but also reduce the risk of developing the devastating symptoms of stroke.

References

1. Murphy SJ, Werring DJ (2020) Stroke: causes and clinical features. Medicine 48: 561-566.
2. Feigin VL, Brainin M, Norrving B, Martins S, Sacco RL, et al. (2022) World Stroke Organization (WSO): global stroke fact sheet 2022. International Journal of Stroke 17: 18-29.
3. Lisabeth LD, Brown DL, Hughes R, Majersik JJ, Morgenstern LB (2009) Acute stroke symptoms: comparing women and men. Stroke 40: 2031-2036.
4. Leifer D (2024) Tenecteplase for Stroke-Opening the Window? The New England Journal of Medicine 390: 760-761.
5. Zhong CS, Beharry J, Salazar D, Smith K, Withington S, et al. (2021) Routine use of tenecteplase for thrombolysis in acute ischemic stroke. Stroke 52: 1087-1090.
6. Teasell R, Salbach NM, Foley N, Mountain A, Cameron JI, et al. (2020) Canadian stroke best practice recommendations: rehabilitation, recovery, and community participation following stroke. Part one: rehabilitation and recovery following stroke; update 2019. International Journal of Stroke 15: 763-788.
7. Grefkes C, Fink GR (2020) Recovery from stroke: current concepts and future perspectives. Neurological research and practice 2: 17.
8. Allison K, Patel D, Alabi O (2020) Epidemiology of glaucoma: the past, present, and predictions for the future. Cureus 12: e11686.
9. Vujosevic S, Aldington SJ, Silva P, Hernández C, Scanlon P, et al. (2020)

ISSN: 2334-2838

Screening for diabetic retinopathy: new perspectives and challenges. The Lancet Diabetes & Endocrinology 8: 337-347.

10. Ang MJ, Afshari NA (2021) Cataract and systemic disease: A review. Clinical & experimental ophthalmology 49: 118-127.
11. Rosenblatt TR, Vail D, Saroj N, Boucher N, Moshfeghi DM, et al. (2021) Increasing incidence and prevalence of common retinal diseases in retina practices across the United States. Ophthalmic Surgery, Lasers and Imaging Retina 52: 29-36.
12. Huang CY, Chen TS, Lin CL, Hu, WS (2017) Does early onset cataract increase the risk of ischemic stroke? A nationwide retrospective cohort study. Internal and emergency medicine 12: 461-465.
13. Fernandez AB, Panza GA, Cramer B, Chatterjee S, Jayaraman R, et al. (2015) Age-related macular degeneration and incident stroke: a systematic review and meta-analysis. PLoS One 10: e0142968.
14. Wang Z, Cao D, Zhuang X, Yao J, Chen R, et al. (2022) Diabetic retinopathy may Be a predictor of stroke in patients with diabetes mellitus. Journal of the Endocrine Society 6: bvac097.
15. Ho JD, Hu CC, Lin HC (2009) Open-angle glaucoma and the risk of stroke development: a 5-year population-based follow-up study. Stroke 40: 2685-2690.
16. Zheng Y, He M, Congdon N (2012) The worldwide epidemic of diabetic retinopathy. Indian journal of ophthalmology 60: 428-431.
17. Buse JB, ACCORD Study Group (2007) Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. The American journal of cardiology 99: 21i-33i.
18. Almutairi NM, Alahmadi S, Alharbi M, Gotah S, Alharbi M (2021) The association between HbA1c and other biomarkers with the prevalence and severity of diabetic retinopathy. Cureus 13: e12520.
19. Chew EY, Davis MD, Danis RP, Lovato JF, Perdue LH, et al. (2014). The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. Ophthalmology, 121: 2443-2451.
20. Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, et al. (2013) Causes of vision loss worldwide, 1990–2010: a systematic analysis. The lancet global health 1: e339-e349.
21. Hill MD (2014) Stroke and diabetes mellitus. Handbook of clinical neurology 126: 167-174.
22. Mosenzon O, Cheng AY, Rabinstein AA, Sacco S (2023) Diabetes and stroke: what are the connections? Journal of Stroke 25 : 26-38.
23. Cai J, Boulton M (2002) The pathogenesis of diabetic retinopathy: old concepts and new questions. Eye 16: 242-260.
24. Cheung N, Rogers S, Couper DJ, Klein R, Sharrett AR, et al. (2007) Is diabetic retinopathy an independent risk factor for ischemic stroke? Stroke 38: 398-401.
25. Chou AY, Liu CJ, Chao TF, Wang KL, Tuan TC, et al. (2016) Presence of diabetic microvascular complications does not incrementally increase risk of ischemic stroke in diabetic patients with atrial fibrillation: a nationwide cohort study. Medicine 95: e3992.
26. Wong KH, Peterson C, Theodore R, Aitken K, Dela Cruz M, et al. (2020) Diabetic Retinopathy and Risk of Stroke: A Secondary Analysis of Accord. Stroke 51: A154-A154.
27. Drinkwater JJ, Davis TM, Hellbusch V, Turner AW, Bruce DG, et al. (2020) Retinopathy predicts stroke but not myocardial infarction in type 2 diabetes: the Fremantle Diabetes Study Phase II. Cardiovascular Diabetology, 19: 1-11.
28. Hankey GJ, Anderson NE, Ting RD, Veillard AS, Romo M, et al. (2013) Rates and predictors of risk of stroke and its subtypes in diabetes: a prospective observational study. Journal of Neurology, Neurosurgery & Psychiatry, 84: 281-287.
29. Hägg S, Thorn LM, Putaala J, Liebkind R, Harjutsalo V, et al. (2013) Incidence of stroke according to presence of diabetic nephropathy and severe diabetic retinopathy in patients with type 1 diabetes. Diabetes care 36: 4140-4146.
30. Pongrac Barlovic D, Harjutsalo V, Gordin D, Kallio M, Forsblom C, et al. (2018) The association of severe diabetic retinopathy with cardiovascular outcomes in long-standing type 1 diabetes: a longitudinal follow-up. Diabetes Care 41: 2487-2494.
31. Tuomi T (2005) Type 1 and type 2 diabetes: what do they have in common? Diabetes 54: S40-S45.
32. Sheybani A, Scott R, Samuelson TW, Kahook MY, Bettis DI, Ahmed IIK, (2020) Open-angle glaucoma: burden of illness, current therapies, and the management of nocturnal IOP variation. Ophthalmology and therapy 9: 1-14.
33. Weinreb RN, Aung T, Medeiros FA (2014) The pathophysiology and treatment of glaucoma: a review. Jama, 311: 1901-1911.
34. Coleman AL, Miglior S (2008) Risk factors for glaucoma onset and progression. Survey of ophthalmology, 53: S3-S10.
35. He Q, Wang W, Xu D, Xiong Y, Tao C, et al. (2024) The association of glaucoma with ischemic stroke and functional outcome after ischemic stroke from the perspective of causality. Cerebrovascular Diseases.
36. Wang M, Chen N, Sun BC, Guo CB, Zhang S, et al. (2023) Association between glaucoma and risk of stroke: A systematic review and meta-analysis. Frontiers in neurology 13: 1034976.
37. Vyawahare H, Shinde P (2022) Age-related macular degeneration: epidemiology, pathophysiology, diagnosis, and treatment. Cureus 14.
38. Ambati J, Fowler BJ (2012) Mechanisms of age-related macular degeneration. Neuron 75: 26-39.
39. Rein DB, Wittenborn JS, Burke-Conte Z, Gulia R, Robalik T, et al. (2022) Prevalence of age-related macular degeneration in the US in 2019. JAMA ophthalmology 140: 1202-1208.
40. Chakravarthy U, Wong TY, Fletcher A, Piault E, Evans C, Zlateva G, et al. (2010) Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC ophthalmology 10: 1-13.
41. Liao D, Mo J, Duan Y, Klein R, Scott IU, et al. (2008) Is age-related macular degeneration associated with stroke among elderly Americans? The open ophthalmology journal 2: 37.
42. Wong TY, Klein R, Sun C, Mitchell P, Couper DJ (2006) Atherosclerosis Risk in Communities Study. Age-related macular degeneration and risk for stroke. Annals of internal medicine 145: 98-106.
43. Tan JS, Wang JJ, Liew G, Rochtchina E, Mitchell P (2008) Age-related macular degeneration and mortality from cardiovascular disease or stroke. British Journal of Ophthalmology, 92: 509-512.
44. Hu CC, Ho JD, Lin HC (2010) Neovascular age-related macular degeneration and the risk of stroke: a 5-year population-based follow-up study. Stroke, 41: 613-617.
45. Taylor TR, Menten MJ, Rueckert D, Sivaprasad S, Lotery AJ (2024) The role of the retinal vasculature in age-related macular degeneration: a spotlight on OCTA. Eye 38: 442-449.
46. Shiels A, Hejtmancik JF (2019) Biology of inherited cataracts and opportunities for treatment. Annual review of vision science 5: 123-149.
47. Chen YC, Liu L, Peng LN, Lin MH, Liu CL, et al. (2013) Cataract surgery utilization after acute stroke: A nationwide cohort study. Journal of Clinical Gerontology and Geriatrics, 4: 7-11.
48. Hashemi H, Pakzad R, Yekta A, Aghamirsalim M, Pakbin M, et al. (2020). Global and regional prevalence of age-related cataract: a comprehensive systematic review and meta-analysis. Eye 34: 1357-1370.
49. Chen Y, Wang W, Liao H, Shi D, Tan Z, et al. (2023). Self-reported cataract surgery and 10-year all-cause and cause-specific mortality: findings from the National Health and Nutrition Examination Survey. British Journal of Ophthalmology, 107: 430-435.
50. Saydah SH, Gerzoff RB, Saaddine JB, Zhang X, Cotch MF (2020) Eye care among US adults at high risk for vision loss in the United States in 2002 and 2017. JAMA ophthalmology, 138; 479-489.