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Review Article

Epidemiology of Stroke

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Abstract

Stroke is more common in older adults, but can occur at any time. In 2009, 34% of people hospitalized with stroke were under age 65. Race and ethnicity contribute to differences in stroke trends: the risk of a first stroke is twice as high for African Americans as for Caucasians. African Americans also suffer the highest stroke death rate in the United States. However, stroke death rates have decreased among all races and ethnicities, with the exception of Hispanics, for whom stroke death rates have increased since 2013. Purpose of the work: To study in detail the factors causing stroke, types of stroke, its epidemiology, as well as treatment options.

Keywords: epidemiology; stroke; brain

Introduction

Stroke is more common in older adults, but can occur at any time. In 2009, 34% of people hospitalized with stroke were under age 65. Race and ethnicity contribute to differences in stroke trends: the risk of a first stroke is twice as high for African Americans as for Caucasians. African Americans also suffer the highest stroke death rate in the United States. However, stroke death rates have decreased among all races and ethnicities, with the exception of Hispanics, for whom stroke death rates have increased since 2013 [1]. Women also have a higher risk of stroke-related death than men, with women accounting for six out of ten people who die from ischemic and hemorrhagic stroke [2]. There are several reasons for this higher risk. One is that women live longer than men on average, and a longer life expectancy increases the likelihood that they will have a stroke. Other unique risk factors that women face include high blood pressure during pregnancy and high blood pressure caused by certain forms of birth control pills. They are also more likely to experience depression and anxiety and often report higher stress levels than men. All of these factors increase the overall risk of stroke in women [3–5]. The trends seen between races in both men and women are also seen when looking specifically at women. African American women are, on average, twice as likely to have a stroke as white women. According to the Centers for Disease Control and Prevention (CDC), this is due to the higher prevalence of high blood pressure, obesity, and diabetes in African American women. These statistics show that across all demographic groups, stroke is an extremely common medical event that needs to be addressed. Two specific types of stroke account for the vast majority of stroke cases. Hemorrhagic strokes are caused by a ruptured blood vessel within the brain, while ischemic strokes are caused by a blockage in an artery in the brain; both conditions cause local hypoxia that damages brain tissue. Although both are serious and common, ischemic strokes are more common, accounting for 87% of all strokes in the United States. Blockages in ischemic strokes are usually caused by blood clots that become lodged in one of the brain's arteries. Currently, tissue plasminogen activator (tPA), a thrombolytic drug that breaks up blood clots, is the only FDA-approved treatment for ischemic stroke. However, a stroke patient must receive this treatment within 4.5 hours of the onset of stroke symptoms [6]. Treatment with tPA outside this therapeutic time window can lead to hemorrhagic transformation, which can cause additional brain damage. If the patient does not reach the hospital within the time window appropriate for tPA treatment, there are other treatment options if the clot does not resolve on its own, including thrombectomy to physically remove the clot. Preventive treatments such as anticoagulants and blood pressure and cholesterol-lowering medications may also be given, as there is an increased risk of a second stroke immediately after a first stroke [1]. Timely administration of these treatments mayhelp reduce the effects of disability that a stroke can cause [7]. Common impairments following a stroke include movement disorders such as hemiparesis (weakness on the left or right side of the body), hemiplegia (paralysis on the left or right side of the body), and central facial paresis [8]. Language and speech impairments such as global or mixed aphasia (impaired understanding of language) and dysarthria (impaired speech) are also common [9, 10]. Other impairments include altered levels of consciousness, impaired vision, and decreased blood flow to parts of the brain [11]. All of these impairments have a dramatic impact on the quality of life of stroke patients. Overall, the treatment options available for ischemic stroke are extremely limited, and more research is needed to not only examine the treatment of this

condition once a patient is admitted to hospital, but also possible recovery options after the event. This review will take a closer look at the risk factors associated with stroke, morphological changes and cellular signaling after stroke, experimental modeling, current treatments and treatments under development for stroke patients.

Stroke Classification

In 2005, a study was conducted to better identify and categorize the causes of ischemic stroke. A widely used system for classifying the causes of stroke is called the Trial of Org 10172 Acute Stroke Treatment (TOAST). The method proposed in the study was called the Stop Stroke Study-TOAST (SSS-TOAST) classification. 50 study participants underwent various imaging tests to determine the likelihood that their conditions would lead to stroke. The probabilities were listed as “certain, probable, or possible” for the tendency of each condition to cause stroke based on a parameter called the positive likelihood ratio (PLR), which “was used to describe the strength of the associations between clinical and imaging features and specific stroke mechanisms” [12]. Mathematically, PLR was defined as "the probability that an individual with a given stroke subtype will have a particular clinical or imaging feature, given the probability that an individual without that mechanism will have the same clinical or imaging feature." There was no statistically significant difference between the TOAST classification system and the SSS-TOAST classification system [12]. In 2011, a new method for stroke causation was published that examined the reliability of the Stroke Causal Classification System (CCS). In the study, twenty members of the International Stroke Genetics Consortium independently assessed the same 50 stroke patients using case abstracts [13]. When comparing the kappa values (which are used to measure interrater reliability [14]) obtained by CCS with those obtained by other classification systems, including TOAST, CCS was found to be the most reliable [13]. However, both CCS and TOAST are well established and remain widely used for stroke causation classification. They are not interchangeable as they require different data and criteria, but the two systems have been found to agree in approximately 70% of cases [15]. Reliable classification of the direct causes of ischemic stroke may lead to improved treatment and medical outcomes for this condition. With a more accurate assessment of the causes of stroke, therapy may be better tailored to prevent or treat ischemic stroke and its sequelae. This review will also cover childhood stroke and perinatal stroke.

Childhood stroke

Stroke is an important cause of neurological morbidity in children; most survivors have permanent neurological deficits that affect the remainder of their lives. Childhood stroke, which is the subject of this textbook, is distinct from perinatal stroke, defined as stroke before 29 days of age, because of its unique pathogenesis reflecting the maternal-fetal unity. Although approximately 15% of strokes in adults are hemorrhagic, half of incident strokes in children are hemorrhagic and half are ischemic. The causes of stroke in children differ from those in adults. Urgent brain imaging is essential to confirm the diagnosis of stroke and guide decisions about hyperacute therapy. Secondary prevention of stroke depends largely on the underlying etiology. Although significant advances have been made in pediatric stroke research over the past decade, the quality of evidence for interventions such as rapid reperfusion therapy, which has revolutionized the treatment of arterial ischemic stroke in adults, remains low. Significant delays in diagnosis and treatment continue to complicate the best possible care. Effective strategies for primary stroke prevention in children with sickle cell disease represent major successes, but barriers to implementation remain. Multidisciplinary members of Childhood Stroke International coordinate global efforts to address these challenges and improve outcomes for children with cerebrovascular disease.

Perinatal stroke

Perinatal strokes are a diverse but specific group of focal cerebrovascular injuries that occur early in brain development and affect approximately 5 million people worldwide. The objective of this review is to describe the epidemiology, clinical presentation, pathophysiology, outcome, and management of 6 subtypes of perinatal stroke. Some perinatal strokes present symptomatically in the first days of life, typically with seizures, including neonatal arterial ischemic stroke, neonatal hemorrhagic stroke, and cerebral sinovenous thrombosis. The remaining subtypes present during the first year of life or later, typically with motor asymmetry, and include arterial presumed perinatal ischemic stroke, presumed perinatal hemorrhagic stroke, and periventricular venous infarction in utero. The sequelae of these injuries include cerebral palsy, epilepsy, and cognitive and behavioral problems, in addition to the psychosocial impact on families. Despite significant advances in understanding the mechanisms of both injury and recovery, much remains to be learned regarding causes and how to optimize outcomes. Perinatal stroke can be divided into 6 specific disease entities based on clinical and imaging criteria. Precise estimates by disease type are lacking, but the overall cumulative incidence is approximately 1:1600–1:2300 live births. The time frame for perinatal stroke includes all cerebrovascular events occurring between 20 weeks of fetal life and 28 days of postnatal life. The neonatal period refers to the first 28 days after birth. Three of the six stroke subtypes that present acutely in the neonatal period, typically in the first days of life, are termed acute symptomatic perinatal stroke and probably account for approximately 50% of perinatal stroke cases. This makes the first week of life the most targeted period of lifelong risk for stroke. The remaining perinatal strokes present outside the first month of life and are collectively termed presumed perinatal stroke because their exact time of onset cannot be determined. Largely due to advances in imaging techniques and increased availability of imaging, most cases that would previously have been labeled as idiopathic hemiparetic cerebral palsy or congenital hemiplegia have been shown to be caused by perinatal stroke. Additional morbidities of perinatal stroke include epilepsy and intellectual, behavioral, and language problems, many of which persist throughout life. This represents a significant socioeconomic time and an economic, social and emotional burden for families. Both acute and delayed manifestations of stroke can be caused by an arterial or venous process that is hemorrhagic or ischemic, or both. Here we discuss each specific type of perinatal stroke, including pathophysiology, presentation, diagnosis and treatment. We conclude with a review of the outcomes common to all types and current rehabilitation strategies to address them, including psychosocial considerations for affected children and their families.

Risk factors

Many pathological and behavioral conditions have been shown to contribute to a higher risk of stroke. These factors include, but are not limited to, diet, smoking, hypertension, and diabetes. Many of these risk factors have a negative impact on the cardiovascular system, which is often the best way to assess stroke risk [16]. Associations have been established between the increased incidence of stroke in younger adults (under 50 years) and traditional risk factors seen in patients over 50 years of age, including conditions such as hypercholesterolemia, hypertension, and diabetes [17, 18]. These conditions and their association with stroke in younger patients have not been as widely studied in the literature. This is because younger patients have certain risk factors or underlying pathologies, such as antiphospholipid syndrome (usually found in women

under 50 years of age), which is a large focus of research in this age group. An increased prevalence of traditional risk factors has been observed in younger stroke victims. The sharpest increases were seen in hypercholesterolemia and hypertension between the ages of 35 and 44 in both men and women. There was also a sharp increase in the development of two risk factors for stroke in the same age group. However, it should be noted that one of the risk factors involved in these statistics was smoking, meaning that for smokers, only one pathological risk factor had to be present for there to be two risk factors. There is excess mortality in each age group across the board for young stroke victims, but again, there is a significant increase in excess mortality in those aged 35 to 50. It is difficult to establish any direct cause and effect from the information reviewed, but there is certainly a correlation between the increase in strokes in younger patients and the increase in the prevalence of certain risk factors at earlier ages that cannot be ignored [17].

One study examining stroke pathology included information on risk factors for stroke patients that were assessed. They studied 27 patients diagnosed with acute ischemic stroke, all between the ages of 65 and 75. Of the 27 patients, 22 had hypertension, which was the most common risk factor observed in the study. The next most common risk factor was atrial fibrillation, which was observed in 14 patients, followed by hypercholesterolemia in 10 patients, coronary artery disease in 9 patients, and diabetes in 8 patients. The study also looked at the family history of cerebrovascular ischemic events for each patient's family and found that 6 of the patients' families had a history of these events. Mortality data were also recorded; 15 patients died within three days of the onset of their ischemic stroke, 4 died four to seven days later, and 8 died eight or more days after their ischemic stroke. Several conditions were named in the study as "predictors" of early mortality, with coma being the most common of these predictors. Other factors included uncontrolled hypertension, diabetes, and acute coronary syndrome. As discussed above, it is difficult to establish any specific causal relationship between the strokes that occurred and the risk factors involved, especially since many patients may have had multiple risk factors simultaneously. The study also suffers from a relatively small sample size, meaning that some of the results may not be generalizable to a larger population [11]. However, the study results are consistent with others that have found a correlation between stroke and several assessed risk factors, such as hypertension, hypercholesterolemia, and diabetes [19–21]. A sedentary lifestyle may also contribute to an increased risk of stroke. Exercise has been shown to be an effective method of stroke prevention, as it reduces both cardiovascular and cerebrovascular risk [22, 23]. Physical exercise also increases the expression of some neuroprotective factors such as endothelial nitric oxide synthase, brain-derived neurotrophic factor, and insulin-like growth factor 1 (IGF-1) [24–26]. In general, many risk factors associated with ischemia are modifiable. Control of factors such as diabetes and hypertension, as well as regular physical exercise, may be important for the prevention of ischemic stroke in high-risk populations.

Modifiable risk factors

Although the overall distribution of IS etiology in young patients may differ from typical age groups, the vascular risk factors that accumulate over time are more consistent with older cohorts. The first and perhaps most unique vascular risk for young patients is smoking. Current smoking is very common among preterm cohorts, occurring in up to 44% of young patients with IS, while it appears to be associated with only ~24% of strokes in older adults [27, 28]. This association is dose-dependent, with increased smoking leading to a corresponding increase in atherosclerotic and cardioembolic strokes [28, 29]. Furthermore, smoking-related risk is not self- sufficient and interacts markedly with other risks, including oral contraceptives and migraine, to exacerbate the overall risk of IS [30,31]. Similar to smoking, hypertension and physical inactivity pose significant risks for increased IS risk [32]. These risks appear to be higher in men and increase in the age ranges 35–44 and 45+, consistent with a shift in stroke risk from women to men [33,34,35,36]. Although it may be less common in younger patients, the risk associated with hypertension is markedly higher than in older patients [37], possibly due to decreased recognition and treatment in younger people [38]. Studies on obesity have yielded conflicting results. Some recent data suggest that obesity predicts a higher risk of IS in the young adult population, with increasing body mass index leading to a progressively higher risk of IS [39–41]. However, other studies have found no significant association between obesity and stroke risk after accounting for other relevant variables [41]. Dyslipidemia is another significant vascular risk factor commonly associated with premature IS, with a higher frequency in men [33,42] and even among children [43]. Despite this general association, the overall mechanism linking lipid profiles to stroke remains somewhat uncertain [44]. This apparent cluster of vascular risk factors is closely interrelated, with smoking promoting hypertension and hyperlipidemia, and a strong association between hypertension and hyperlipidemia [45,46]. However, it should be noted that each of these factors has been shown to be more prevalent in men and tends to have the greatest impact in the 35–55 year age group, where stroke is more common in men [33,42]. Young women may be at a distinct set of risks. Pregnancy stands out as a clear gender-specific risk in younger age groups; however, current data associate it with <5% of strokes in young women [37,48]. Oral contraception and hormone replacement therapy also increase stroke risk via thromboembolic mechanisms [50,51,49]. A recent meta-analysis showed a dose-time relationship between oral contraceptive use and stroke, with each 10 μg dose increase and each additional 5 years of use increasing the risk of stroke by 20% [52]. These factors provide significant age-dependent risks for women, contributing to the increased prevalence of stroke among women in the youngest age groups.

Genetic and non-modifiable risk factors

From the current discussion, we see that modifiable risk factors associated with young IS generally cluster into hypertension and pregnancy/hormones. Although these are independent risks, they may increase the risk associated with genetic factors and chronic diseases. Since a significant number of IS in young people are attributed to cryptogenic or other etiologies, there may be multiple underlying conditions contributing to the risk of IS. Of particular interest are conditions such as migraine with aura, atrial fibrillation (Afib), Fabry disease, Moyamoya disease (See these syndromes+ PFO) and connective tissue diseases. PFO is relatively common. Most estimates suggest that it may occur in approximately 27% of the general population, with varying reported sex differences [53, 54, 55]. The incidence in patients with cryptogenic stroke is much higher, and it has been found in 62.6% of young strokes of unknown etiology [56,57]. In addition, PFO also interacts with pregnancy and other thrombotic risks [58]. Given the relatively high prevalence of PFO in the general population, its true causal relationship with IS in young adults is a matter of ongoing debate [59]. However, observational data report that PFOs are associated with stroke in patients without other risk factors [60], and surgical closure may reduce the risk recurrent stroke in young patients. Although both PFO closure and anticoagulation appear to reduce IS, the use of long-term anticoagulation in young adults may increase the risk of bleeding disorders [61, 62]. Similar to PFO, Afib poses an increased risk of embolism due to disruption of regular blood flow, likely exacerbated by other larger systemic abnormalities. There is evidence that PFO contributes to atrial vulnerability, increasing the likelihood of arrhythmias [63]. In the context of stroke in young adults, the incidence of Afib is

much lower; however, it still poses a significant risk for IS [64]. Similar to older populations, diagnostic challenges of Afib, primarily due to paroxysmal episodes, may lead to its underdiagnosis [65]. An association has also been found between Afib and migraine with aura compared to migraine without aura [73]. Migraine itself also poses an increased risk of cardioembolic stroke, with migraineurs having vascular dysfunction [67]. The overall prevalence of migraine with aura is higher in young women, and the existing risk of IS is exacerbated by other factors such as smoking and oral contraceptive use [68,69]. Fabry disease is a lysosomal storage disorder that results in thickening of large vessels [70]. Although Fabry disease is rare (1 in 100,000) in the general population, 24–48% of patients with Fabry disease will experience stroke, especially at a young age (28–54 years) [71,72]. While Fabry disease is hereditary, the cause of Moyamoya disease is unknown. Moyamoya, which causes progressive narrowing of the cranial arteries, primarily affects people under 50 years of age and is more common in low-income and urban areas. Risks also appear to be increased among women, people aged 18–44 years, and Asian/Pacific Islanders, with a particularly high prevalence noted in Japan . [73,74] Although moyamoya is more strongly associated with IS risks, it also carries an increased risk of bleeding. Just as PFO is associated with cryptogenic stroke, and Fabry disease and moyamoya disease are associated with atherosclerosis, connective tissue disorders may contribute to cervicospinal dissection. A number of conditions may be assessed here, including Ehlers-Danlos syndrome, fibromuscular dysplasia, and Marfan syndrome. These are genetic disorders that increase blood vessel fragility and subsequent stroke risks . This increases the risks associated with trauma and may lead to cervical artery dissection. Although options for mitigating these risks are limited, a recent opinion highlights the need to assess possible traumatic triggers in young patients with potential stroke [75]. It should be noted that the risk of premature stroke has a hereditary component even in the absence of recognized genetic conditions.

What is premature stroke?

In the current literature, the terms “premature stroke”, “early stroke”, and “stroke in the young/ young stroke” are used interchangeably. This may be because there is no clear definition of what constitutes premature stroke. In addition, there is no uniform definition of “young” age. While the lower age limit is fairly uniform at 18 years, the upper limits span the decade between 45 and 55 years, with 45 and 50 representing the most commonly chosen limits. These limits are below the critical age of 55 years, after which the incidence of stroke doubles with each subsequent decade of age. In addition, they represent the lowest quartile of the overall stroke age distribution, the median of which is 60–65 years. To provide a more comprehensive assessment, we consider this topic in the broader age range of 18–55 years, which covers most of the relevant studies. As is the case in the elderly, IS typically accounts for the largest proportion of stroke cases (44–65%) among younger patients, followed by intracerebral hemorrhage (ICH; 17–39%) and subarachnoid hemorrhage (SAH; 16–20%).

Age and gender

Young-onset stroke accounts for 10–15% of all stroke patients. However, heterogeneity among young adults is high and may present analytical challenges. Although convenient, treating the 18– 55 age group as a monolith may miss shifts in risk factors and etiologies across stages of adult life. Stroke incidence is age-specific even among young adults, with incidence increasing exponentially across the 15–50 age range. It may therefore be useful to examine the epidemiology of stroke in young adults by subgroups of 18–34, 35–45, and 46–55 years. Although stroke is rare in the 18–34 age range, women are 26–56% more likely to develop premature stroke than men, depending on stroke subtype. From age 35 onwards, overall stroke incidence increases, with men (compared to women) at increasingly higher risk of stroke. This age-related increase in stroke risk among men is largely explained by traditional risk factors. Stroke subtype also appears to change with age. The proportion of lacunar and large arterial strokes increases in patients over 40 years of age, whereas cardioembolic, cryptogenic, and “other” stroke types decrease. In populations with intracerebral hemorrhage, recent significant increases in incidence rates have been found in patients in the 18–44 and 45–64 age ranges over the past two decades. The effects of age and sex-modified stroke risk in young people have been largely reported in high-income countries. It is likely that different patterns of differential stroke risk between men and women will be observed in global data.

Race and Ethnicity

In blacks and African Americans, the risk of stroke is 2–5 times higher across subtypes [76–79], with differences appearing to be greatest in the 35–44 year age group. Particular increases have been noted for lacunar stroke, driven by an increased prevalence of hypertension among African Americans [80]. These findings are markedly associated with geography. Studies from Europe report generally similar trends, although to a lesser extent [81]. Studies from the Caribbean offer contrasting evidence, suggesting that the increased prevalence found in black and African American cohorts may be driven primarily by socioeconomic and environmental variables [76]. Black patients who experience premature strokes have higher rates of hypertension, type II diabetes, and congestive heart failure [83]. Similar available evidence suggests that Hispanic cohorts have higher rates of stroke than non-Hispanic whites [77,84].

Experimental models of ischemic stroke

In vivo models

Many experiments studying the mammalian response to stroke have been conducted primarily in rodents such as mice and rats. In order to conduct these experiments, a situation must arise that mimics a stroke in the animal. The most common methods are middle cerebral artery occlusion (MCAO) procedures, and there are several different MCAO methods that are used in research. The MCAO method most commonly used in research is the intraluminal suture model, in which a suture is fed into the middle cerebral artery from either the external or internal carotid artery to block blood flow for a period of time, resulting in a temporary occlusion [84,85]. This model produces a large volume of infarcted tissue and has played an important role in the progression of stroke research regarding issues such as blood-brain barrier disruption and the inflammatory response to ischemia [86,87]. Direct occlusion of the middle cerebral artery occurs via craniectomy. In this method, occlusion is typically accomplished by clamping the artery when reperfusion is required, or by cauterizing and transecting the artery when permanent occlusion is required. Craniectomy models can be used in many species, making it a popular model for simulating ischemic stroke [84]. The photothrombosis model is another occlusion method that is frequently used in both rats and mice. Briefly, rose bengal, a light-sensitive dye, is injected systemically into the animal. Following injection, a 532-nanometer laser is directed directly onto the animal's skull, causing the dye to react [88]. This results in the formation of reactive oxygen species (ROS), which damage the endothelial lining of the vessels. A commonly proposed mechanism for clot formation is that endothelial cell injury initiates the contact pathway of the coagulation cascade, and that platelet aggregation occludes the artery [89,90]. However, some have questioned the role of platelet activation in clot formation, and some authors have suggested that the model is not suitable for studying stroke, but only for studying the blood–brain barrier [91,92]. This model has many advantages, including

reproducibility, the ability to select the region of the brain that tolerates occlusion, and low mortality in animals undergoing the procedure [84]. Another commonly used method for modeling stroke in vivo is the use of endothelin-1, a potent vasoconstrictor. The peptide can be applied in several ways, including directly to the exposed vessel, to the brain surface, or by injection into the brain. The duration and level of occlusion can be altered by varying the concentration of endothelin-1 used in the treatment. Endothelin-1 models are used in both mice and rats, and although they are typically used for short-term experiments [93,94], they are generally more useful for long-term recovery studies [84]. While these models certainly have their advantages, the fact that hundreds of stroke therapy attempts have failed to translate to human treatment shows that much remains to be done to accurately recreate ischemic conditions in experimental models. Each of the above models has its advantages, but all have significant drawbacks that undermine the potential for translation of stroke therapies to human treatment. For example, the intraluminal thread MCAO model often involves very sudden reperfusion rather than the gradual one seen in ischemic stroke in a clinical setting. This results in the activation of different pathways that more closely resemble global ischemia, making the translation of the results to human studies extremely difficult. Other drawbacks include the potential for hemorrhage into the blood vessels, induced hyperthermia in the animal, and the possibility of incomplete occlusion of the artery [84,95]. The main drawback of direct occlusion models via craniectomy is the amount of trauma that must be inflicted on the brain to gain access to the middle cerebral artery. Along with the cranial trauma, there are the possibilities of direct brain damage during the craniectomy procedure, as well as the problems that may arise from exposing the brain to the open atmosphere. The potential for temperature change in the exposed part of the brain, as well as the disruption of intracranial pressure, are very different from the occurrence of stroke in humans. In addition to these drawbacks of the model, it shares the same drawback as the intraluminal thread model, namely that reperfusion occurs suddenly, causing activation of a different set of pathways [84]. The photothrombotic model has only two major drawbacks in terms of recreating ischemic conditions, one of which is the absence of a penumbra region in the area surrounding the ischemic region. This makes it extremely difficult to assess whether treatments have any effect on the volume of damaged tissue in the stroke model. However, many attempts have been made to overcome this drawback. One such attempt is a modified photothrombotic model published in 2016, in which the penumbra can be defined using a combination of perfusion-weighted imaging, diffusion-weighted imaging and other MRI technologies [88]. The results were promising, and if the definition of a penumbra similar to that in humans becomes easily achievable, one of the major problems of this model will be solved. Another problem with the model is that the photothrombotic model induces both vascular and cytotoxic edema, whereas human ischemic strokes primarily induce cytotoxic edema that does not immediately breach the blood-brain barrier, meaning that even if penumbra identification is achieved, there may still be difficulties in translating to human treatment [84]. The endothelin-1 model also has several shortcomings. Ischemia begins slowly and edema forms very weakly.

Endothelin-1 also affects astrocytes, neurons, and can induce axonal sprouting, all of which may cause discrepancies compared to human strokes [84,95]. Although there have been some successes in stroke research using the above models, the huge lack of translation of these models to human strokes is a major reason why new effective stroke treatments remain unclear. There is much room for improvement in these areas of preclinical research, and until these models can more accurately illustrate strokes in humans, it may be difficult to find new therapeutic strategies to combat ischemic stroke.

In vitro models

In vitro models are also widely used in ischemic stroke. Many of these models involve co-culture of different cell types, such as astrocytes and endothelial cells. Using co-culture, it is possible to mimic certain properties of the blood-brain barrier and study how different cell types interact with each other under ischemic conditions [96]. Other in vitro models use primary cultures taken from animal brain tissue. These cultures can be useful for studying the effects of different treatments on specific aspects of the brain, such as neurons in the cerebral cortex [97]. Both types of in vitro models are used to study specific cellular responses to conditions comparable to ischemia, such as oxygen and glucose deprivation. These models have several advantages because they allow researchers to directly study both animal and human cells [98]. Because species differentiation is key in translating findings from the lab bench to the bedside, the use of human-based in vitro models can aid in understanding the differences between human and animal responses to stroke. However, in vitro studies, important as they are, need to be combined with in vivo studies to obtain a complete picture of ischemia in humans [84].

Modern methods of treatment of ischemic stroke

As mentioned above, tPA is the only FDA-approved treatment for ischemic stroke. Endogenous tPA is a serine protease that plays an important role in the body's fibrinolytic system. Thrombi are formed by the aggregation of platelets on fibrin networks that form after vessel injury. tPA initiates the process of clot dissolution by activating plasminogen to plasmin, which cleaves fibrin and dissolves clots. tPA is regulated by binding to fibrin, which increases the catalytic capacity of tPA. The recombinant form of tPA was approved as a drug in 1996 after a clinical trial by the National Institute of Neurological Disorders and Stroke tPA Stroke Study Group was published the previous year. The study showed a 30% relative risk reduction in the likelihood of no or little disability compared with placebo at 90 days . The therapeutic time window for tPA is extremely narrow, as it must be administered within 4.5 hours of the onset of stroke, otherwise there is a high risk of hemorrhagic transformation, which can cause other complications with treatment. Unfortunately, some are hesitant to administer tPA even within the therapeutic time window, as there are other risks that come with it, including anaphylaxis and systemic bleeding, and clinical trials are still underway to determine what risk factors should disqualify someone from receiving tPA treatment for ischemic stroke. There have been attempts to widen the therapeutic time window for tPA. If the window can be widened, it would give patients more time to get to the hospital and be seen by a doctor for tPA treatment. Combination therapy with tPA has been studied in preclinical settings to try to achieve this goal. One study evaluated the use of the Rho kinase inhibitor Fasudil loaded into liposomes and administered two hours before tPA administration in rats. The stroke model used was photothrombotic occlusion of the middle cerebral artery. The study showed that treatment with Fasudil-loaded liposomes (Fasudil-Lip) and tPA reduced the amount of damaged tissue in the rat brain compared to treatment with Fasudil alone, Fasudil-Lip alone, and tPA alone. With this treatment, the therapeutic time window for tPA treatment in rats was significantly increased to 4.5 hours, more than double that of tPA alone (the study found the therapeutic time window for tPA administration in rats to be just under 2 hours). As mentioned earlier, most stroke patients do not arrive at the hospital in time to receive tPA treatment. Additionally, patients who arrive at the hospital in a timely manner should still be evaluated to rule out the possibility that they are suffering from a hemorrhagic stroke, which cannot be treated with tPA, as it will lead to further bleeding in the brain. Since tPA is the only drug currently available to treat ischemic stroke, it is critical to give

patients as much time as possible to receive tPA in the hospital after their arrival. Extending the therapeutic time window may save patients from severe disability or death when they may not have arrived within the current therapeutic time window for tPA administration. A rapidly growing area of stroke recovery research involves the use of microRNAs (miRNAs) to control gene and protein expression in the brain after stroke. It is estimated that up to 30% of human protein-coding genes canregulated by microRNAs. MicroRNAs are thought to play a central role in embryonic development, cellular differentiation, and metabolism, and have been used in research to treat cancer, liver disease, and heart disease. Additionally, one microRNA- based treatment for hepatitis C has already entered phase II clinical trials, demonstrating the great potential this area of research holds. Briefly, mature microRNAs integrate into a multi-protein structure called the RNA-induced silencing complex (RISC) and bind to the 3' untranslated region of the target mRNA. This process can block translation or cleave the target mRNA, resulting in decreased expression of the corresponding protein. miRNAs are thought to play an important role in the progression of ischemic stroke pathology through changes in the expression of select miRNA, such as miR-15a, which promotes ischemic injury through the inhibition of BCL-2, an anti-apoptotic gene. BCL-2 family genes have been a major focus of miRNA therapy research in ischemic stroke, as they play a central role in cell death and are regulated by several miRNAs after ischemia, such as miR-29, miR-181, and the aforementioned miR-15. A specific example of a potential therapeutic approach is blocking miR-181 activity after ischemic stroke in mice using an antagomir, a designed oligonucleotide that binds to the region of the mRNA targeted by the miRNA of interest, preventing the regulation of the desired mRNA by the miRNA. The study found that administration of miR-181a antagomir after MCAO resulted in decreased NF-κB expression, increased BCL-2 levels, and reduced infarct size. Long-term recovery of treated mice was also improved. While these results are promising, miRNA research is still relatively new and comes with its own set of challenges. A single miRNA can target a number of different mRNAs, and while this aspect has the potential benefit of silencing multiple harmful mRNAs with a single miRNA, there is also the potential for unwanted side effects due to unintended targeting of beneficial mRNAs. In addition to potential issues with target specificity, efficient delivery and rapid degradation of miRNA also pose potential challenges, the solutions to which are still being explored. However, despite these hurdles, miRNAs represent a promising area of potential treatments that could have a significant impact on the treatment of ischemic stroke.

Morphological changes and signaling after stroke

Another important aspect of stroke research is the assessment of morphological changes in the brain after ischemic stroke. Different types of brain cells undergo unique morphological changes after the onset of ischemia. The ischemia observed in stroke patients causes damage to several types of cells in the brain, including neurons, glial cells, and blood vessels. In particular, neurons in the center of the ischemic area undergo liquefaction necrosis, a process that has been observed in other ischemic stroke studies in which the cell body and axons of neurons disappear. Large neurons exhibit edema, vacuolization of the neuroplasm, and disappearance of the nucleus and nucleolus. The shapes of smaller neurons become distorted, and the cell nucleus becomes compacted. These symptoms indicate severe damage to organelles, including mitochondria, which no longer function properly and are unable to produce energy for the cell. These symptoms are also seen in glial cells, astrocytes, oligodendrocytes, and microglial cells. The penumbra, which contains viable neurons surrounding the ischemic area, also has what are called “red neurons” or “ischemic neurons.” These neurons are characterized by several factors, such as acidophilic cytoplasm, changes in neuronal proteins, and the breakdown of endoplasmic ribosomes and Nissl bodies. Lymphocytes, granulocytes, and “rare macrophages” have been found in both ischemic and penumbra areas. This indicates that processes involving cell apoptosis in these areas lead to the recruitment of these cells and an immune response. The migration of these cells from blood vessels into the ischemic region has been noted in numerous studies and has become a starting point for further investigation into the potential roles that monocytes play in ischemic conditions. In addition, increased permeability of both capillaries and the blood-brain barrier is observed in the penumbra, ischemic core, and other areas, leading to perivascular and perineuronal edema. Blood-brain barrier changes occur rapidly after ischemic stroke. The development of marked extravasations and perivascular edema often occurs. Increased permeability of the blood-brain barrier leads to an influx of serum protein between four and six hours after stroke, and also leads to vasogenic edema. Vasogenic edema peaks between one and two days after stroke, and tissue water content increases by more than one hundred percent. During the first three days after stroke, there is little response from blood-borne leukocytes. During this period, astrocytes undergo reactive gliosis (astrogliosis), a common occurrence in central nervous system injury. In the healthy central nervous system, astrocytes are a diverse group of cells that exhibit variability in both morphology and functionality as they regulate several different physiological processes, including regulation of blood flow, delivery of energy metabolites to neurons, and participation in synaptic function. They also regulate ion and fluid balances and direct the maintenance of transmitter molecules. In central nervous system injury, astrocytes undergo changes in both molecular expression and morphology. This response is not an all-or-nothing reaction, as it occurs in a series of steps that can be attenuated at different stages. The changes may result in altered gene expression or reversible changes in morphology, or they may be permanent changes such as those that lead to scarring. The extent to which astrocytes respond to injury to the central nervous system is mediated by both extracellular and intracellular signaling mechanisms that direct the responses. The goal of the response is to protect neurons and limit both inflammation and infection around the affected area. This process is necessary to support neuronal recovery in the penumbra of the injury. Unfortunately, it is also accompanied by adverse effects that are often harmful to the patient. Astrogliosis has been observed to contribute to or cause further problems in the central nervous system, whether by producing new, deleterious effects or by losing existing functionality. Microglial cells, also called macrophages in the brain, also undergo transformations following ischemic stroke. They become swollen and secrete inflammatory proteins such as cytokines, chemokines, proteases, cyclooxygenase-2, ROS, prostaglandins, HO-1, and other metabolites, resulting in the consumption of damaged tissue from the ischemic core. However, these inflammatory factors can also be toxic to surrounding cells, as will be discussed in detail later in this section. The brains of patients who die between four and seven days after stroke show evidence of neuronal damage both within and outside the ischemic region, demonstrating the potential for extended stroke coverage of the central nervous system. During the same time period, neurons present in the gray matter appear to be more susceptible to damage from hypoxia compared to neurons in the white matter. In addition, many large macrophages are already actively phagocytosing dead tissue at this time, which is widespread in both the ischemic and penumbral regions. Neuronal cell apoptosis is most common in the first few days after stroke. By assessing the number of cells that express caspase proteins (caspase is a well-known marker of cells undergoing apoptosis), it was noted that the number of cells undergoing apoptosis was lower in patients who died after

three days, suggesting that most of the apoptosis occurs in the early Time after stroke. The inflammatory response of the brain to ischemia is another aspect of stroke that is of great interest to research. This process involves the cells that mediate the response, as well as any factors, such as cytokines or proteins, that are released that may affect surrounding tissue. Cells that originate from both the brain and the blood play a role in the inflammatory response in the brain. Microglial cells are the main immune cells in the central nervous system and can become activated within minutes of an injurious event. They reach peak activity two to three days after injury and persist for several weeks afterward. The role that these cells play in ischemia is not well understood, as there are several types of microglia that perform different functions. One example of this is that microglia have been observed to secrete both neuroprotective and neurotoxic factors after injury. Astrocytes are also integral to brain function, but like microglial cells, they exhibit duality in their function following ischemia. As mentioned above, astrocytes undergo astrogliosis, in which they detect glial fibrillary acidic protein (GFAP) and begin secreting factors that both complicate and enhance ischemic recovery. Other cells that play an inflammatory role migrate to the brain from the blood. Leukocytes are the first to arrive at the ischemic site. They are responsible for the release of neurotoxic factors including inducible nitric oxide synthase and matrix metalloproteinases (MMPs), which are associated with both increased blood-brain barrier breakdown and hemorrhagic transformation following ischemic stroke. Research suggests that neutrophils are more detrimental than beneficial to recovery from ischemic stroke, as removal or exclusion of neutrophils has been shown to reduce injury and improve recovery. Monocytes and macrophages also migrate to the brain via the bloodstream and, like microglial cells and astrocytes, have a complex relationship with the inflammatory response to stroke. Blood monocytes fall into two categories when it comes to inflammatory responses: anti-inflammatory and pro-inflammatory. Anti-inflammatory monocytes are so named because they produce anti-inflammatory cytokines such as interleukin 10 (IL-10). Pro- inflammatory monocytes are so named because they secrete factors such as IL-1β and tumor necrosis factor (TNF-α), both of which are known to have neurotoxic effects. Monocytes have been observed to differentiate into dendritic cells or cells similar to microglia and macrophages upon reaching the brain. Blood macrophages fall into similar categories with respect to the inflammatory response; generally, M1 macrophages are considered proinflammatory and M2 macrophages are anti-inflammatory. Like monocytes, these cells secrete both the proinflammatory factors IL-1β and TNF-α and the anti-inflammatory factors IL-10 and transforming growth factor beta (TGF-β) consistent with their M1/M2 phenotype. Lymphocytes also migrate to the brain after ischemic stroke. T cells have been a focus of research because many of their types have been linked to the response to ischemia. Of particular interest are CD4+, CD8+, and γδT cells, which secrete cytokines such as IFN-γ and IL-17 that are harmful to the brain. However, regulatory T cells produce cytokines with anti-inflammatory properties such as IL-10, indicating that T cells, like blood monocytes and macrophages, have a complex relationship with the inflammatory response to ischemia that needs to be studied in more detail. Cytokines released by these cells have profound effects on certain aspects of inflammation and recovery after stroke. Some of the effects seen with these cytokines are beneficial, some are detrimental, and some are not fully understood. Beneficial cytokines include IL-10, TGF-β, TNF-α- inducible protein 8-like-2 (TIPE-2), and IGF-1, all of which have been shown to reduce the amount of tissue damage following ischemia. Cytokines that have a detrimental effect on recovery and are associated with increased lesion volume are being studied more frequently. These include IL-1α, IL-1β, and E-selectin, adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1), and chemokines such as monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), and fractalkine (CX3CL1). These cytokines mediate injury in a variety of ways. Some examples include the contribution of IL-1β to blood-brain barrier disruption and vasogenic edema, the promotion of inflammation by adhesion molecules that cause neutrophils to adhere to the vascular endothelium and infiltrate the injured site, and the ability of CX3CL1 to activate and recruit microglia to the injured brain region. Other cytokines appear to play conflicting roles in the response to ischemic stroke. For example, TNF-α is most often considered a pro-inflammatory factor and plays an important role in glutamate excitotoxicity because it blocks glutamate transporters on astrocytes and increases the surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at glutamatergic synapses. However, studies report that TNF-α has both pro-inflammatory and neuroprotective tendencies. One explanation for this duality that is being explored is the relationship between these responses and the two receptors to which TNF-α binds. However, TNF-α is not the only cytokine with contradictory effects. MMP-9 also has different effects depending on the time point at which it is released. It is associated with increased blood-brain barrier permeability, edema, and hemorrhagic transformation in the early stages of the post-stroke period, but in later stages it induces several growth factors that stimulate angiogenesis. The cytokine P-selectin also plays a dual role in ischemia: blocking P-selectin reduces brain damage, but also reduces the survival of animals that undergo middle cerebral artery occlusion (MCAO) experiments. Given these examples, it is clear that more research is needed to understand exactly how these cytokines affect the brain in relation to ischemic stroke. There are several pathways that are responsible for the release of these cytokines at the site of ischemia. These include the Toll-like receptor (TLR) pathway, the mitogen-activated protein kinase (MAPK) pathway, and the nuclear factor kappa B (NF-κB) pathway. TLRs have been closely associated with ischemic stroke in animal models. Inhibition of TLR2 and TLR4 in particular has been shown to reduce susceptibility to brain injury following ischemia in mice, showing smaller volumes of infarcted tissue. However, other studies have shown that stimulation of TLRs prior to ischemic injury may have neuroprotective effects by inhibiting TNF-α, one of the end products of the TLR2 pathway. Early stimulation of this pathway actually inhibits the expression of NF-κB (the precursor of TNF-α) and enhances the expression of IFN-β, which is a precursor to anti-inflammatory cytokines . Unfortunately, it is unlikely to be used as a preventative measure for ischemic stroke, as the pathway alteration must occur before the stroke occurs, which is difficult to predict in advance. MAPK pathways are also closely associated with ischemic stroke, as all of these pathways are activated during ischemic stroke. Their exact role in ischemic stroke is unclear, but studies have shown that pathways involving JNK and p38 contribute to ischemic injury, as inhibition of these pathways reduces the amount of damaged tissue. These pathways promote the production of pro-inflammatory cytokines such as TNF-α and IL-1β. However, some of the MAPK pathways may also have neuroprotective properties. Activation of ERK1 or ERK2 may be beneficial, as they increase the expression of the Bcl-2 protein, which prevents apoptosis. The ERK5 pathway may also act as a neuroprotector when activated before an ischemic event. Another set of pathways activated after an ischemic event are the NF-κB pathways, which are responsible for the induction of pro-inflammatory factors such as MMPs. Activation of the p50 and p65 pathways has been shown to be detrimental in ischemic stroke. Studies also show that p50 knockout mice had less tissue damage in a permanent stroke model. However, some studies are again conflicting, as inhibition of NF-κB with diethyldithiocarbamate in rats resulted in DNA fragmentation and higher tissue damage volumes.

Identifying the changes that cells undergo after ischemia, especially signaling changes in the brain, has been one of the most challenging aspects of stroke research. A better understanding of the mechanisms that are significantly involved in post-stroke pathology could significantly contribute to the development of treatments for ischemic stroke.

Diagnosis and treatment

Due in part to their rarity, premature strokes carry an increased potential for misdiagnosis, particularly among patients younger than 35 years and those with posterior circulation strokes. Studies report headache and peripheral vertigo as the most common symptoms leading to misdiagnosis of posterior circulation strokes. However, such misdiagnoses may also be attributed to the actions of emergency medical personnel rather than to neurology-based assessments. Up to 50% of young people with overt stroke-like symptoms may not have a stroke mimic. Thus, diagnostic accuracy is extremely important in young patients with stroke symptoms, and expanded use of magnetic resonance imaging (MRI) to confirm suspected stroke should be considered. Similar to stroke in the elderly, treatment of premature strokes is driven by specific stroke types and etiologies. In the acute phase of IS, thrombolysis and reperfusion strategies remain the most effective options. Given the diverse etiologies, a more thorough diagnostic workup may be warranted in younger patients with IS. Subsequent treatment is aimed at avoiding complications and promoting recovery. Secondary stroke prevention strategies will overlap with stroke in the elderly but are largely driven by the specific stroke etiology. For example, antithrombotic (antiplatelet or anticoagulant) therapies should be considered following dissection. Statin use after IS is also associated with lower mortality rates and reduced stroke recurrence. Although established treatment and secondary prevention strategies remain effective in younger populations, younger patients are more likely to experience delays in presenting to emergency services, seeking appropriate care, and receiving an accurate diagnosis, which complicates treatment and compromises recovery . The interaction of socioeconomic factors with delayed or suboptimal care also requires special attention. For example, unhealthy patients tend to have longer reperfusion times. Perhaps the most effective way to reduce the time to premature stroke is to develop targeted primary prevention strategies implemented within a robust public health infrastructure. These may include smoking cessation, awareness and appropriate treatment of hypertension and dyslipidemia, and improved diet and lifestyle.

Regenerative therapy for Future Research

The use of stem cell therapies has been explored in a wide range of conditions [83], including neurological diseases and autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease, in which inflammation plays a key role . Transplantation of hematopoietic stem cells (HSCs) with CD34+, CD133+, and CXCR4 phenotypes, which are derived from human umbilical cord blood, has been investigated as a therapy for myocardial ischemia, and cardiac function has been improved in rat models. However, therapies that involve transplantation of CD34+ HSCs require millions of stem cells, so a method for rapidly generating stem cells ex vivo is required for these therapies to be plausible. A procedure for rapid expansion of CD34+ HSCs using aminated polyethersulfone (PES) nanofibers as scaffolds has already been developed. Using this method, a 225-fold expansion was achieved without inducing differentiation, indicating that the development of sufficient numbers of stem cells ex vivo should not be a barrier to further development of potential stem cell therapies. Expansion using this procedure yielded sufficient numbers of cells treated to overexpress proangiogenic factors for transplantation to treat limb ischemia injury by neovascularization. Neural differentiation of CD34+ HSCs has been studied in relation to the treatment of neurological diseases such as Parkinson's disease (PD) and dopaminergic neuron loss. In the study, mice were subjected to induction of brain injury by administration of 1 methyl-4-phenyl-1, 2, 3, 6-tetrahydropyrine (MPTP mice). CD34+ HSCs were expanded using PES nanofibers as a scaffold. A total of 4.5 million cells were obtained from an initial number of 20,000. They were then differentiated in vitro in a medium containing neural differentiation factors for three weeks. Successful differentiation was characterized by the presence of neural markers such as GFAP, MAP2 and oligo2, as well as nestin, none of which were expressed in undifferentiated cells, which were used as a control. Differentiated cells also changed morphology starting from day 3 and became very similar in appearance to glial cells and neurons. Following peripheral administration of neurally differentiated HSCs, reconstitution of dopaminergic neurons as well as angiogenesis were observed in both the caudate nucleus/ putamen and the substantia nigra pars compacta of the MPTP mouse brain, showing great promise for stem cell therapy of neurological diseases. These current advances in stem cell research and the study of the effect that stem cells have in PD models indicate that stem cell therapy has great potential for success in the treatment of ischemic stroke. Dental pulp stem cells (DPSCs) are also of interest for the treatment of neurodegenerative conditions. In particular, they show great potential to promote neuroregeneration after injuries such as ischemic stroke. Because they originate from the neural crest, they are prime candidates to replace neuronal cells lost in neurodegenerative conditions such as ischemic stroke. In a study published in 2017, DPSCs were seeded in Matrigel with hippocampal slices taken from adult mice. When co-cultured with hippocampal slices, DPSCs did differentiate along the neuronal lineage as expected, but they also secreted neurotrophic factors that supported the growth and maintenance of hippocampal tissue . Another study conducted on 3-day-old rats demonstrated the ability of DPSCs to integrate into the injured brain. Neurally predifferentiated DPSCs were transplanted intrathecally after induced injury by applying a metal stamp cooled to -60˚C to the skull above the forelimb motor complex. The labeled cells were localized to neuronal progenitor zones in the rat brain and were also found in the injured part of the brain four weeks after injury. These cells also displayed neuronal markers such as NeuN and GFAP, as well as voltage- dependent ion channel activity . Although the study does not mimic ischemic stroke conditions, the successful integration of predifferentiated DPSCs into the injured rat brain is a promising result and requires further testing in a scenario mimicking ischemic stroke, which is already being studied. Due to the success of advanced methods for expanding and differentiating HSCs and DPSCs, stem cells represent a class of potential stroke treatments that is being widely studied. Successful expansion, differentiation, and evidence of neuronal regeneration and angiogenesis with CD34+ HSCs, as well as experiments using DPSCs, indicate that stem cells have great potential for inclusion in stroke research. Although the development of new treatments remains unclear in ischemic stroke research, there are still many treatment avenues that can be explored more thoroughly. From combination therapy with tPA to stem cell therapy and manipulation of inflammatory factors, there are still many strategies that can be explored in the treatment of ischemic stroke.

Conclusion

Stroke epidemiology remains one of the key areas of research in neurology and public health. In the course of this work, many factors contributing to the development of stroke were analyzed, including genetic, modifiable, non-modifiable, environmental. Understanding these factors is crucial for the development of effective prevention and treatment strategies. The data obtained confirm that stroke is a

multifactorial disease, and its prevalence varies significantly depending on the geographical characteristics of the population. An important task is to gain access to quality medical services, as well as to conduct educational activities for the population on preventive measures. In addition, today there is a need for further research aimed at studying the long-term consequences of stroke, as well as the effectiveness of new rehabilitation methods. Future research should also focus on interdisciplinary approaches to stroke prevention, including the integration of knowledge from medicine and epidemiology, as well as sociology. In conclusion, stroke is a serious public health problem, and approaches to its study and prevention should be comprehensive and based on current scientific data. This will not only reduce morbidity and mortality, but also improve the quality of life of stroke survivors and their families.

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