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NARRATIVE REVIEW

Stroke as a neurodegenerative disease; a review of the introduction, epidemiology, diagnosis, complications and causes

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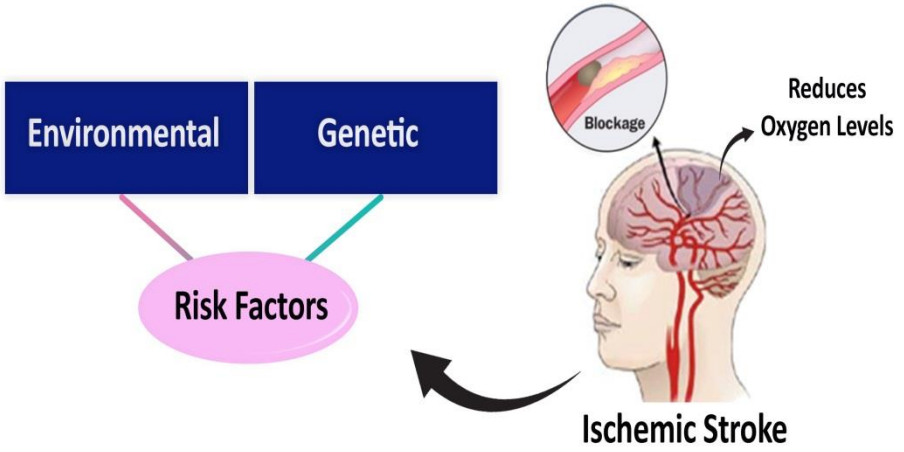
Highlights

- Cerebral ischemia is one of the most common neurological diseases that is one of the main causes of death worldwide.
- Ischemic stroke is caused by obstruction of blood supply to brain tissue, which reduces oxygen levels and damages brain tissue.
- The interaction of environmental and genetic factors changes the risk of stroke.

Graphical Abstract



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Abstract

Ischemic stroke is a cardiovascular disease that accounts for many deaths and disabilities in developed and developing countries. Stroke can be an ischemic, hemorrhagic, or transient ischemic attack (TIA). Ischemic or obstructive stroke is one of the most common types of stroke that is caused by an obstruction in the arteries supplying blood to the brain. This blockage reduces blood flow and oxygen to the brain leading to damage or death of cells. Failure to re-establish blood circulation can lead to permanent brain damage. Blood tests, electrocardiograms, CT scans or MRIs, vascular imaging, and electroencephalograms are some of the methods used to diagnose ischemia. Major risk factors for stroke such as obesity, diabetes, hypertension, high cholesterol, hyperlipidemia and atherosclerosis have been well established. However, the exact mechanism of stroke is not yet fully understood and may be due to the complex interactions of environmental and genetic factors. Among the genetic factors, there are variants related to the regulation of biosynthesis and catabolism of fats and cholesterol. Given the importance of this issue, the purpose of this study reviewed the epidemiology, diagnostic methods, complications and causes of stroke.

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Introduction

Stroke is currently the second leading cause of death and the first leading cause of disability worldwide (1). The prevalence of stroke mortality is about 250 to 300 people per 100,000 of the total population in Asian countries. It is estimated that there are approximately 28.5 million cases of disability due to stroke that results in loss of normal life (2). About 60% of survivors of stroke need care for their daily activities. More than 80% of strokes are ischemic and are caused by the cessation of blood supply to the brain tissue by the closure of cerebral arteries due to the formation of blood clots or emboli (3). Studies have shown that an increased incidence of stroke is associated with lifestyle changes, decreased physical activities and factors such as obesity, high fat intake (4, 5), air pollution (6) and smoking (7). In addition, some genetic factors are involved in the development or increase of susceptibility to ischemic stroke.Previous studies have shown that genetic polymorphisms in several key genes including phosphodiesterase 4D (PDE4D) (8), ALOX5AP (8, 9), FADS1/FADS2 (10), IL-6, IL-1B (11) and PCSK9 are associated with an increased risk of ischemic stroke (12).

Hypercholesterolemia with autosomal dominant inheritance is a common hereditary single gene disorder that leads to cardiovascular disease by increasing serum low-density lipoprotein (LDL). Autosomal dominant hypercholesterolemia (ADH) is caused by mutations in the two significant loci encoding the LDL receptor and the apolipoprotein B100 receptor, its natural ligands.ADH is also caused by a mutation in the PCSK9 gene (Proproteinconvertasesubtilisin/Kexin type 9), a vital enzyme that modulates cholesterol homeostasis and encodes Nurc-1 (a regulator of neuronal apoptosis-regulating convertase) (12). There is evidence that PCSK9, combined with LOX-1 (a lectin-like receptor), plays an essential role in hyperlipidemia, atherosclerosis, and ultimately ischemic stroke. The LOX-1 protein is encoded by the OLR1 gene, which belongs to the E sweeper receptor family. This protein is responsible for the absorption and transport of oxidized LDL into macrophages and, ultimately, its cessation (13). Recent studies have shown that this protein plays a vital role in the pathophysiology of atherosclerosis. Loss of function of the LOX-1 protein causes the absorption of oxidized LDL into vascular endothelial cells and leads to the formation of toxic compounds that can cause atherosclerosis (14). However, PCSK9 is an enzyme that binds to the LDL receptor. The LDL receptor removes blood cholesterol. The binding of PCSK9 to the LDL receptor will increase the concentration of cholesterol in the blood. Studies show that PCSK9 plays an essential role in blood cholesterol homeostasis (15).

Stroke death rates vary from country to country, depending on social class and geopolitical region. There are significant geographical differences in the prevalence of stroke deaths worldwide. There are also differences in the type of stroke that occurs, the frequency distribution of ischemic stroke subtypes, and the stroke mechanism between whites and Asians. For example, carotid artery cerebral haemorrhage has been reported more frequently in Asians (16). In industrialized countries, the prevalence of stroke is 5 per 1000 population, but it is around 5-10 per 1000 population (17). Despite numerous epidemiological studies, population-based information is still scarce in developing countries (18). In recent studies on the differences between women and men, the overall incidence of stroke in men was 33% higher than women, except in a few studies that had a small sample size and poor results (19). In Europe, the annual incidence of stroke is 1 to 2.9 per 1,000 men and 0.6 to 1.9 per 1,000 women (20). With epidemiological changes and ageing, the proportion of strokes may also increase. In general, the prevalence of stroke in urban areas is higher than in rural logic, and the levels of disability and dependence in stroke survivors are significantly higher in urban areas (20).

Over the past 20 years, significant advances have been made in the diagnosis and treatment of stroke. However, it is still the fifth leading cause of death in the United States and the leading cause of long-term disability. Stroke affects about 795,000 people a year, with an average of one stroke every 40 seconds and one death every 4 minutes. Hospitalized stroke patients are considered to have a 5 to 10% mortality rate for ischemic stroke and 40 to 60% for hemorrhagic stroke, and only 10% of survivors fully recover. Approximately 87% of all strokes are of ischemic origin, caused by a blockage in a cerebral artery. Approximately 13% of strokes are hemorrhagic due to damage or rupture of blood vessels in the cerebral parenchyma (ICH) or the subarachnoid space (subarachnoid haemorrhage) (21).

The incidence of stroke in Iran is also not pleasant. Iranian specialists say people in Iran get a stroke 10 years earlier than in other countries. Meanwhile, the share of Iranian men is 25% higher than women. The representative of the Iranian Stroke Association, noting that 100,000 people in Iran suffer from stroke annually, said: "The significant reduction in the age of onset of stroke in the country is alarming (22). Some review papers described the features of stroke (23, 24), and we decided to narrate this topic in a slightly different manner. Due to the importance of the subject, in this study, we will have an overview of the introduction, diagnosis, complications and causes of stroke.

Stroke

In ancient medicine, a stroke was a sudden attack with the loss of consciousness and the patient's senses, resulting in death. In modern medicine, the term stroke may refer to a brain stroke or heart attack (25). Stroke is a sudden neurological disorder accompanied by loss of consciousness or disturbance in the patient's senses. The occurrence of stroke leads to long-term disability or death (25). It starts suddenly. Initially, the severity of neurological disorders may be high, a phenomenon seen in embolic stroke. Or it may progress from a few seconds to a few hours (sometimes days), which may be due to progressive arterial thrombosis or recurrent embolism. A stroke that develops actively (but not as a result of cerebral edema) directly due to underlying vascular disease is called a developing stroke or a progressive stroke. Slow-growing localized brain disorders (over weeks or months) are unlikely to be due to stroke and are more likely to indicate a tumor or inflammatory or degenerative disease (25, 26).

Ischemic or obstructive stroke is one of the three most common types of stroke. Also known as cerebral ischemia or obstructive stroke. This type of stroke is caused by an obstruction in the arteries that send blood to the brain. This blockage reduces blood flow and oxygen to the brain, leading to damage or death of brain cells. If blood circulation is not restored quickly, brain damage can become permanent (27). Ischemic stroke, which includes thrombotic and embolic types, is one of the leading causes of death worldwide. Stroke is the third leading cause of death in the United States and one of the most common causes of hospitalization. Despite significant advances in treating acute ischemic stroke (including thrombolytic and mechanical resection or disintegration of the clot), these interventions are often appropriate for less than 5% of patients due to lack of timely referral for treatment (28).

A transient stroke (TIA) is a transient, unstable condition of a part of the brain that occurs due to impaired blood flow to the brain. It can be stated that when the blood supply to the brain is disrupted, but the time and severity of this disorder is not enough to lead to a stroke (death of part of the tissue) is called transient ischemic attack (29, 30). Hemorrhagic stroke (ICH) is caused by blood leakage or ruptured arteries in the brain. In this condition, blood leaking from the arteries can damage the brain cells by squeezing them. Rupture of cerebral arteries can be caused by complications such as hypertension, trauma, Anticoagulants, and aneurysms. Severe hypotension, less than 13-14 mm Hg within 6 hours, suddenly causes acute internal bleeding or ICH (31). Figure 1 shows the types of strokes.

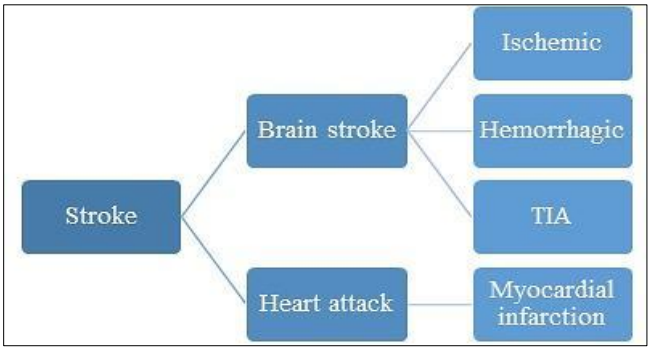

Figure 1. Types of strokes. Stroke is divided into two types, brain stroke and heart attack. A brain stroke can be an ischemic, hemorrhagic or transient ischemic attack (TIA). Nevertheless, a heart attack is caused by myocardial infarction (32).

Ischemic stroke symptoms

Stroke is a syndrome characterized by the acute onset of neurological symptoms for 24 hours. Neurological symptoms are caused by central nervous system involvement as a result of impaired cerebral blood flow. The site of involvement is guessed by the symptoms, identified by neurological examination, and confirmed by imaging (CT or MRI).In case of acute onset of symptoms and often in whenthe patient is old which there are risk factors for stroke, as well as in cases where the signs and symptoms can be limited to the blood supply for a specific blood vessel in the brain, the vascular cause of stroke should always be considered. Intended if the stroke is confirmed using imaging, further investigations will be performed to determine the causes (33).

In many cases, history and neurological examination provide enough information to locate the lesion on one side of the brain and the anterior or posterior circulation (33). The specific symptoms of an ischemic stroke depend on the area that is damaged. The general symptoms that are common in most ischemic strokes are shown in Figure 2.

Figure 2. Ischemic stroke symptoms. Ischemic stroke can include vision problems, paralysis, dizziness, or aphasia, depending on the area in the brain affected (34).

Ischemic stroke causes

Clot

An ischemic stroke occurs when a blood clot or fat plaque blocks an artery that carries blood to the brain. This obstruction can appear in the neck or skull. Clots usually start in the heart and travel through the circulatory system. A clot can be removed individually, or it can form in the artery itself. When this clot blocks the artery, the brain does not receive enough blood and oxygen, and its cells begin to die (35).

Fat plaques

Fat-induced ischemic stroke occurs when fat plaque separates from an artery and reaches the brain. Plaque can also form in the arteries that carry blood to the brain, blocking the arteries and causing an ischemic stroke (35). Complete ischemia, which is a severe form of stroke than normal ischemia, occurs when the flow of oxygen to the brain is significantly reduced or completely stopped. This is usually caused by a heart attack but can also be caused by other conditions such as carbon monoxide poisoning (36).

Risk factors and complications of ischemic stroke

Circulatory system conditions constitute a significant risk factor for ischemic stroke. It's because these conditions increase the risk of clots or fat deposits. These conditions include atherosclerosis, high cholesterol, blood pressure disorders, and atrial fibrillation. But other risk factors include obesity, smoking, diabetes, stress, some drugs like cocaine and alcohol. It is now known that obstructive stroke is more common in people who have a family history of stroke or have had a stroke before. Men are more likely than women to have an obstructive stroke, and the risk of stroke increases with age (37). Risk factors for transient ischemic attack include family history, gender (men more likely), age, previous history, sickle cell anaemia, and black race (38). It is now well established that genetic profile plays a vital role in the susceptibility to stroke. The role of some factors involved in the coagulation system and the role of some inflammatory factors such as cytokines in the occurrence of stroke have been proven. For example, IL-6 is one of the most studied cytokines related to inflammation in stroke.

Some studies have mentioned this inflammatory mediator as a beneficial and harmful factor (39). Some studies have also shown that the FOXF2 gene increases the risk of stroke due to small vascular disease in the brain (40, 41). Studies to investigate the changes in gene expression in ischemic stroke in mice have also shown that during the seven days after stroke, 12 gene groups had the most changes in expression compared to control conditions, including genes related to Functional immediate early gene groups, transcription, heat shock proteins, inflammation, apoptosis, cytoskeleton, metabolism, growth factors, message pathways, ion channels, neurotransmitter receptors, and synaptic proteins (42, 43, 44). Medical complications after stroke are common and strongly affect the results. These include infections (especially pneumonia, aspiration, and urinary tract infections), cardiac arrhythmias, gastrointestinal bleeding, pulmonary embolism, and depression. In some cases, such as arrhythmias and depression, complications are directly due to brain damage (45).

Diagnostic tests

Blood test

This test should be done routinely to detect the treatable causes of stroke and rule out other mimics. Recommended tests include 1- Complete blood count: A complete blood count can identify possible causes of stroke (such as thrombocytosis, polycythemia, sickle cell disease). For unknown reasons, a high white blood cell count at the time of admission is an independent factor that exacerbates the outcome of stroke. 2- Inflammatory markers include increased erythrocyte sedimentation rate (ESR) and increased CRP (C-reactive protein). 3- Serum glucose: Determination of blood sugar is critical because hypoglycemia or hyperglycemia can manifest as focal neurological symptoms and stroke imitation. Hypoglycemia with focal symptoms, seizures, or coma requires immediate glucose administration to prevent permanent brain damage, and hyperglycemia (non-ketone hyperosmolar hyperglycemia or diabetic ketoacidosis) requires immediate, specific treatment. 4.Serum lipids: Total cholesterol and HDL measurement helps to assess risk factors for stroke (46, 47).

Electrocardiogram

ECG should be performed routinely to detect latent myocardial infarction or cardiac arrhythmias such as atrial fibrillation contributing to embolic stroke (48).

Scanning or MRI

A routine CT scan or MRI should be done to differentiate between infarction and bleeding as a cause of stroke to rule out other lesions (such as tumors and abscesses) because they mimic the symptoms and also discover the location of the lesion. Contrast-enhanced CT scans are usually preferred for early diagnosis because they are widely available, rapid, and easily distinguish between ischemia and bleeding (49).

Vascular imaging

It's a type of imaging to identify the underlying structural causes of cerebrovascular disease and to determine the surgical lesions of the extra-cranial carotid artery in patients. Digital subtraction angiography, magnetic resonance angiography to diagnose moderate to severe extra-cranial carotid artery stenosis, Doppler ultrasonography for internal carotid artery stenosis, carotid plaque imaging such as high-resolution MRI and Dopplerultrasonography suspected stenosis of the internal carotid, middle or basilar artery, are methods that are used for diagnosis (49).

Electroencephalogram (EEG)

EEG is rarely valuable for assessing stroke. However, it may help to differentiate between seizures and TIA in some patients for whom there is no other way to differentiate these conditions (50).

Stroke epidemiology

The World Health Organization (WHO) estimates that 15 million people have a stroke each year, of which 5 million remain permanently disabled. In the absence of population-based interventions, 7.8 million deaths are projected to occur by 2030. However, due to the increase in world population, the highest mortality rate in the world is related to stroke, from 89 per 100,000 in 2005 to about 98 per 100,000 in 2030, where the increased incidence of brain stroke is more pronounced. Worldwide, strokes show significant changes in mortality. Between 1970 and 2008, there was a 42% reduction in stroke incidence in high-income countries, compared with a 100% increase in stroke in the middle- and low-income countries (51). The number of strokes in Iran is not very pleasant either. Iranian specialists say people in Iran get stroke 10 years earlier than in other countries. Meanwhile, the share of Iranian men is 25% higher than women. The representative of the Iranian Stroke Association, noting that 100,000 people in Iran suffer from stroke annually, said: "The significant reduction in the age of onset of stroke in the country is alarming" (22).

Conclusion

Stroke is a disease characterized by the acute onset of neurological symptoms for 24 hours. Neurological symptoms are caused by central nervous system involvement as a result of impaired cerebral blood flow. Studies have shown that increasing the incidence of stroke is associated with lifestyle changes, decreased physical activities, and other factors such as obesity, high fat intake, air pollution, and smoking. The main risk factor for ischemic stroke is the condition of the circulatory system. Conditions such as atherosclerosis, high cholesterol, hypertensive disorders, and atrial fibrillation are among the common factors associated with the circulatory system. Of course, factors such as obesity, smoking, diabetes, stress, certain drugs such as cocaine and alcohol consumption are also among the risk factors. In addition, some genetic factors are involved in the development or increase of susceptibility to ischemic stroke. Genetic changes in several essential genes, including phosphodiesterase 4D (PDE4D), ALOX5AP, FADS1 / FADS2, IL6, IL1B, and PCSK9, are associated with an increased risk of ischemic stroke.

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