

A Short Review: Genetic Risk Factors of Stroke

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A B S T R A C T

A stroke happens when an artery in the brain gets blocked or ruptured, which results in the death of a brain tissue area because of a loss of its blood supply (brain infarction). Most strokes are ischemic strokes caused by ischemia due to arterial occlusion, but some are hemorrhagic strokes caused by an arterial rupture. Transient ischemic attacks have been considered similar to ischemic strokes. However, they cause no permanent damages to the brain, and their signs usually resolve during 1 h., which are sometimes called mini-strokes. As for hemorrhagic strokes that cause a blood clot, that is, that deprives brain cells of blood supply, and therefore enough oxygen and glucose, the damage depends on the length of time the brain cells are deprived of blood, for example, If brain cells are deprived of the blood for only a short period of time, they can be slightly damaged, but if brain cells are deprived of blood for a longer period, the cells may die, and thus the patient loses some body functions, sometimes permanently. High blood pressure has been defined as the leading risk factor for strokes, and there are other factors like smoking, high blood cholesterol, obesity, atrial fibrillation, diabetes, and others. Strokes are more common among the elderly than younger adults because of the risks of injuries that result in causing strokes with age. Statistics have indicated that over 2/3 of the strokes happen in people who are older than 65, while the rates of strokes in men are very slightly higher than women, but more than 60% of stroke deaths occur in women, and this may be because women They have a stroke at a slightly higher (average) age than men. Black people have a higher possibility of getting a stroke than white people.

1. Introduction

Stroke or cerebrovascular accident or stroke can be defined as the sudden onset of a neurological deficit that lasts for longer than 24 h. that occurs when one of the arteries in the brain gets ruptured or blocked, which results in the death of a brain tissue area because of the loss in its blood supply and causing sudden symptoms (1). The brain cannot store oxygen but instead relies on a network of blood vessels to supply it with oxygen-rich blood, but when a stroke occurs, a deficiency in the blood supply occurs, which causes the nutrients and oxygen to be cut off from nearby nerve cells, which die 3 to 4 minutes after the oxygen is cut off (2).

A stroke can occur in the event of a severe narrowing of an artery as a result of the accumulation of fatty deposits in it.

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The blood clot is in an artery already suffering from the narrowing, and stroke can also be caused by other pathological conditions such as sudden bleeding in the brain or sudden bleeding in the spinal cord. It is known as hemorrhage in the sub-arachnoid arteries, atrial fibrillation, cardiomyopathy, or blockage of small arteries in the brain (3). Stroke can also be caused by other conditions such as sudden hemorrhage in the brain, sudden hemorrhage in the spinal cord, so-called hemorrhage in the subarachnoid arteries, atrial fibrillation, cardiomyopathy, or blockage of small arteries in the brain. Most strokes are ischemic (caused by ischemia due to an arterial occlusion), but some are hemorrhagic (caused by an arterial rupture) (4). Occlusion of the carotid arteries is a narrowing of the carotid arteries, which is usually caused by atherosclerosis, which is caused by the accumulation of cholesterol, fats, and other substances when they pass in the bloodstream, such as cells caused by inflammation and the remains of cells, proteins and calcium. These substances stick to the walls of blood vessels and collect with age to form what is called Fatty deposits

or plaque that accumulate and narrow the carotid arteries, putting the patient at risk of stroke (5).

2.The Concept and Functions of Brain

The brain is located inside the bones of the skull and communicates with the remaining parts of the body by the cranial nerves (passing through openings of the skull) and spinal nerves passing from the spinal cord over small orifices between the spine bones and control arms, legs and trunk, and consists of three main regions: the cerebellum, the trunk, and brain and cerebral hemisphere (6). The cerebellum is considered as the center of control for balance and movement coordination. The brainstem controls breathing, heart rate and essential reflexes such as coughing, a reaction to clearing the airways, and these two parts of the brain seem to provide minimal brain power for survival, and the right and left hemispheres are connected. These two parts of the brain control the ability to speak, think, complex movements, and vision(7).

The right and the left hemisphere are communicated by bundles of nerve fibers that pass from one side of the body to the other (6). Blood flows to the brain through 4 main blood vessels that contain two vertebral and two carotid arteries, and the two vertebral arteries enter the skull through the vertebral column and supply blood mainly to the brainstem and the cerebellum (8).

The shape of a semi-circle contributes to maintaining an adequate flow of blood in the event of an artery blockage. Unfortunately, the effectiveness of arterial circle varies from one person to another and usually does not protect people from stroke symptoms in the event of blockage of one of the main arteries(9).

3. The Concept of Stroke

A stroke is the sudden onset of some neurological deficit that lasts more than 24h that occurs when an artery in the brain gets blocked or ruptured, which results in the death of a brain tissue area because of the loss of its blood supply (10). The brain cannot store oxygen, but rather relies on a network of blood vessels to supply it with oxygen-rich blood, but when a stroke occurs, the blood supply is insufficient (9).

A stroke occurs as a result of severe narrowing of the artery due to the accumulation of fatty deposits or the separation of a small part of the fatty deposits and its movement to smaller arteries in the brain, or as a result of the formation of a blood clot in an artery that is already narrowed, and a stroke can also be caused by other pathological conditions such as sudden bleeding in the brain or sudden hemorrhage in the spinal cord, or what is known as hemorrhage in the arachnoid arteries Sub-atrial fibrillation, cardiomyopathy, or blockage of small arteries in the brain (11).

4. Types of Strokes

There are 2 stroke types:

4.1. Ischemic Stroke

About 80% of ischemic strokes, which are in some cases, referred to as mini-strokes, are considered as an early warning factor for stroke, which is caused by an arterial blockage, that is, preventing brain cells from perfusion, and therefore the insufficient oxygen and glucose that are transported by the blood. The damage done depends on the length of time Depriving brain cells of blood, if brain cells are deprived of blood for a short period, it can be slightly damaged, but if brain cells are deprived of blood for a longer period, it may die and the patient may lose some body functions, sometimes permanently(12). The most common types of ischemic strokes are:

4.1.1. Thrombotic Stroke

It is an ischemic stroke type, which indicates that part of the brain has been injured because of the blockage of the artery usually supplying the blood to it, which is why the blood flow is decreased or stopped in total (13). Blood clotting often happens in areas damaged by atherosclerosis, an illness where arteries are affected by the accumulation of fatty deposits (9). This procedure happens in a head artery located at the back of the neck and responsible for the blood supply to the brain, similar to the other arteries in the brain and neck area (14).

4.1.2. Stroke Embolic

Y (13). An embolus is the body or debris that travels through the blood and implants in a blood vessel and blocks it, and this is in contrast to a clot or thrombus, which forms at the point of blockage in a blood vessel and does not move from one place to another, while 20% of strokes are of the hemorrhagic type, which is the second type of stroke means that it results from bleeding in the brain or around the brain (15). In such stroke type, a blood vessel is ruptured, which results affect the normal blood flow, and blood leaks to or around the tissues of the brain. This bleeding occurs as a result of high blood pressure. Another less common cause of bleeding is a ruptured blood vessel, an arteriovenous malformation (16).

4.2. Hemorrhagic Stroke

4.2.1. Intervertebral Hemorrhage

In this type of stroke, a blood vessel within the brain is ruptured and the blood flows to the tissue of the brain that surrounds it, which causes damages to the brain cells (17).

4.2.2. Subarachnoid Hemorrhage

In this type of stroke, the bleeding starts in a large artery or the brain surface area, and the blood flows to the space between the skull and the brain. Such bleeding type is often accompanied by a sudden and strong headache (18). A high number of factors can increase the risks of strokes, and some of those factors could also result in increased risks of stroke (cardiac arrest) (AMI-Acute Myocardial Infraction). Other factors increase stroke

risks, including age, hypertension, hypercholesterolemia, smoking, diabetes, obesity, and heart disease (19).

5. Causes of Stroke

5.1. Arteriosclerosis

Atherosclerosis is a common problem that affects the arteries, and it can occur at an early age that begins with fatty spots and begins to appear in the wall of the blood vessel. These spots can cause enough damage to cause a blood clot inside the artery, which leads to its narrowing and restriction of blood flow, and blood clots can also block the blood vessel and become the cause of the stroke (17). There is a possibility of reducing the risks of developing atherosclerosis through making lifestyle changes. Switching to a low-fat diet, eating fresh fruits and vegetables daily, and exercising all contribute to protecting against the risk of atherosclerosis(20).

5.2. Hypertension

Most people realize that high blood pressure is harmful to health, but few know that high blood pressure increases the risks of stroke. When blood is pushed through the circulatory system with great pressure, the walls of the arteries receive blows that damage them, so atherosclerosis and blood clotting become more likely (21).

Blood pressure is measured in two phases of the heart's palpitation cycle: systolic and diastolic blood pressure, and researchers are aware that in the case where the blood pressure is increased and stays at a certain level, decreasing the level of the blood pressure will result in reducing risks of the stroke. Recent studies have shown that changes in the rate of blood pressure contribute to strokes more than keeping the pressure level constant, as high blood pressure from time to time in what is known as pathological hypertension carries with it an increased risk of stroke. Experts currently recommend keeping the blood pressure below (140/85) and considering it the most ideal. As for people who suffer from diabetes, lung problems, or vascular diseases, experts advise them to keep their blood pressure below (130/80) (22).

5.3. Smoking

The majority of people are aware of the harm of smoking to their health, but not many realize how harmful it is (19). Recent studies have shown that approximately 50% of smokers will prematurely die from smoking-related illnesses (like a heart attack or chronic obstructive pulmonary diseases, stroke, and lung cancer) (23). The possibility of early death due to these problems and the risk of strokes or heart attacks can be reduced if one quits smoking, as nicotine replacement therapy such as patches and chewing gum can help quit smoking, and they are available in pharmacies with no prescriptions (24).

5.4. Heart Disease

Atrial fibrillation represents the most common heart issue, increasing the risk of stroke (25). This disease is common among the elderly and affects one out of twenty people over the age of sixty-five (25). The problem happens when the heartbeat is irregular, which increases the risk of blood clots that form in the heart, and blood clots may lead to a stroke in the case where they travel through the circulation from the heart to the brain (26). The problem can be treated with anticoagulants such as warfarin, and this is one of the best treatments as it reduces the incidence of stroke significantly (27).

5.5. Cerebral Hemorrhage

Among its other names is Cerebral Hematoma or Intracranial Hematoma. This bleeding occurs inside the cranium, but it occurs in the brain tissue or in the ventricles (24). Symptoms include headache, unilateral weakness, and vomiting, decreased levels of consciousness, a stiff neck and fever. Bleeding appears in both the brain tissue and the ventricles (28). Causes include cerebral injury, intracranial aneurysms, arteriovenous malformations, and brain tumors(27). The major risk factors for bleeding represent high blood pressure. Some other factors of risk include alcohol, hypocholesterolemia, use of anticoagulants, and cocaine use. The diagnosis is typically made using computed tomography(28).

5.6. Rupture of Blood Vessel

Sometimes the blood vessels in the neck may rupture, which may result in causing a stroke in the case where one of the arteries is blocked, or blood clots occur. It is worth noting that the carotid artery transports blood to the brain mainly from the front of the neck, and that artery may be damaged as a result of a strong blow to the neck as a result of Injury during exercise or a car accident, and other accidents (29).

5.7. Normal Blood Clotting

It is one of the most important rare genetic problems in blood clotting (such as deep venous thrombosis), so the patient must be subjected to medical examinations, especially if the patient suffers a stroke (29).

5.8. Pills to Prevent Pregnancy

The contraceptive pill causes a woman to have a stroke, although the risk is relatively low. If 10000 females take contraceptive pills for 1 year, an average of 1 woman will get a stroke (30). These numbers have been based upon using a combined estrogen-progesterone pill. The risk is more than three times higher compared to a woman of the same age who does not take birth control pills, and the risk appears to increase more if the woman is a smoker (30). Although this risk is doubled, the risk of stroke is minimal because stroke is rare in women of childbearing age, and the risk is small compared to other risks associated with pregnancy. In general, the benefits of birth control pills outweigh the risk of stroke(31).

5.9. Hormone Replacement Therapy

The Hormone replacement therapy may lead to problems similar to those caused by birth control pills (32). Major clinical trials showed the benefits and risks of this treatment (33). The use of estrogen and progesterone (in women who retain the uterus) and progesterone alone (in females that had a hysterectomy) have been related to a slightly increased risk of stroke (33).

5.10. Use of Prohibited Substances

Prohibited substances of all kinds and illegal athletic performance-enhancing drugs can cause strokes in young adults. Unfortunately, the number of strokes caused by the use of illegal substances is on the rise, although such cases can be avoided(33).

5.11. Migraine

Migraine is a very common disease, but it is not clearly understood, and its very common symptoms are seeing a flash and a strange sensation in the arms, face and legs, and these attacks may sometimes cause temporary weakness (34). In very rare cases, migraine attacks cause physical weakness that may be permanent, known as a migraine stroke (32). Very rare types of hereditary strokes, stroke that affects young men may be due to genetic problems, and it has recently been proven that there is a syndrome of this type of families, knowing that this syndrome is very rare and causes multiple strokes and is known as autosomal dominant encephalopathy syndrome with infarcts Subcortical and leukemic encephalopathy (34).

6. Stroke Inheritance

Stroke is defined as the 3rd most common one of the causes of death and the main cause of long-term neurological disability worldwide. The conventional factors of vascular risks for the stroke only play a role in approximately 40% - 50% of the stroke risks, so the genetic factors play a role in a significant rate of the stroke and could be polygenic or monogenic, monogenic disorders (one gene) may be responsible for about 1% of all ischemic strokes (24). The monogenic stroke disorders include some conditions like cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), an increasingly well-known clinical syndrome. The CADASIL causes sub-cortical lacunar infarction and dementia in over 80% of the cases. CADASIL may be similar to micro-vascular diseases due to hypertension (Binswanger's disease) (37). CADASIL Symptoms tend to appear between ages between 40 and 60, about 30% of the patients with migraine with Aura Common mood disorders. Neuropathological findings include smooth muscle hypertrophy of the small arteries, demyelination, and glia in the subcortical white matter and basal ganglia, given That the dominant genetic

basis of this disease CADASIL is linked to the notch-3 family gene on the 19th chromosome (38).

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) single gene disorder that directly affects the cerebral small blood vessels and results from the mutations of HTRA-1 gene, which encodes HtrA Protease / Peptidase Serine (HTRA-1) (34). CARASIL is the second known genetic form of the ischemic, nonhypertensive, cerebral small-vessel disease with an identified gene and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) currently (35).

The main CARASIL manifestations include the stroke or the progressive deterioration in brain function, progressive dementia, early baldness, and acute episodes of low back pain (32). CARASIL is characterized by atherosclerosis, especially small arteries, without granulations or amyloid deposits. CARASIL can be described as a prototype for the single-gene disorders of cerebral small vessels that are secondary and distinct from the CADASIL (36). The CARASIL-related mutant HTRA-1 had shown decreased protease activities and failed to suppress growth factor signaling transduction, which indicates that the increase in the signaling results in causing CARASIL arteriopathy, so HTRA-1 represents a gene for cerebrovascular small vessel disease and spinal disease (24).

Moreover, other monogenetic conditions like sickle cell and the Fabry disease result in causing stroke as well (35). Those single-gene disorders either lead to small vessel or macro-vascular strokes (or a combination of the two) and play the role of beneficial models to understand and study the conventional strokes and cerebrovascular diseases and their co-morbidities like vascular dementia for human monogenic disorders associated with stroke (35). A medical study concluded that the incidence of stroke has a genetic origin. If one of the parents had a stroke at the age of sixty-five, the probability of children having the same disease increases four times when they reach this age. Researchers at Boston University have emphasized the importance of knowing the history Patients of the parents are carefully treated because this helps to treat the patient before his medical condition worsens if he shows early stroke symptoms(36).

7. Single gene disorders with Stroke

The ischemic stroke is a presenting characteristic of several single-gene disorder types. Aetiology in those cases is multifactorial. Whereas the conventional inheritance forms can't be proved, the latest evidences strongly suggest the significance of the genetic factors (37). The focus will be directed towards some single-gene disorders that are related to the ischemic strokes, which include: Evidences from the epidemiological researches as well as the animal models, as well as the study of candidate genes that link specific genes to stroke risk, have

finally described a number of the uncommon Mendelian traits that arise from the defect in a single gene in which stroke is prominent (38).

These diagnoses should be considered for any patient with stroke, the diagnosis is often aided by distinct clinical phenotypes, in particular, in presence of family history of the early strokes (39). Cerebral infarction results from 1 of many pathophysiological mechanisms that may be affected by a defect in a single gene, and those include heart valve disorders, large arterial diseases, blood disorders, vascular diseases, connective tissue disorders and mitochondrial disorders that lead to the arterial dissection(38).

8. Genes Associated With Stroke

Polygenic or multifactorial effects in which multiple genes exert little or risk of influence on the phenotype, with individuals presenting with different combinations of genetic and environmental influences (40). completed and population stratification that these genetic factors may exhibit. However, recent research indicates that these challenges may not be impossible to overcome (40). CADASIL or autosomal dominant cerebral arteropathy with subcortical infarctions and leukoencephalopathy, is the only form of ischemic stroke isolated for the purpose of familial genotypes in which the responsible gene is identified. There are also many individual genetic disorders in which stroke genes are involved that have been identified (41). CADASIL showed at least four of the features, namely, lacunar stroke, cognitive deficits, migraine headache and psychiatric disorder (depression), which may precede the onset of stroke (42). The disease most commonly appears in the forties but can appear from the twenties to the seventies, the diagnosis can be made by genetic testing or skin biopsy, it has been shown that CADASIL results from high mutations in Notch-3 gene that inactivation of CADASIL, as a result of which the usual number of six residues is converted to a single number, resulting in abnormal polymorphism of Notch3, although after more than 50 different mutations have been reported, no clear correlations between Genotype and phenotype (42).

9. Conclusions

The article examined genetic risk factors for stroke, types of stroke including hemorrhagic stroke and ischemic stroke, as well as stroke-causing subtypes. Studies have confirmed that fat is a risk factor for atherosclerotic stroke, as atrial fibrillation and atrial heart disease are associated with heart attacks. High blood pressure, smoking, diabetes and other major risk factors for stroke, as many clinical trials have shown many medical treatments to reduce the risk of stroke, and it has been shown that low blood pressure, statin treatment, anticoagulants,

revascularization in the carotid artery, and changes Diet, quitting smoking and physical activity all reduce the risk of infection.

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الخلاصة:

تحدث السكتة الدماغية في حالة انسداد أو تمزق أحد الشرايين في الدماغ مما يؤدي إلى موت منطقة من نسيج المخ بسبب فقدان إمدادها بالدم (احتشاء الدماغ). معظم السكتات الدماغية عبارة عن سكتات دماغية إقفارية ناتجة عن نقص التروية بسبب انسداد الشرايين، ولكن بعضها عبارة عن سكتات دماغية نزفية ناجمة عن تمزق الشرايين. تم اعتبار النوبات الإقفارية العابرة مشابهة للسكتات الدماغية الإقفارية، ومع ذلك فهي لا تسبب أضرارًا دائمة للدماغ وعادةً ما تختفي علاماتها خلال ساعة واحدة والتي تسمى أحيانًا السكتات الدماغية الصغيرة، أما السكتات الدماغية النزفية التي تسبب جلطة دموية أي تحرم خلايا الدماغ من إمداد الدم، وبالتالي ما يكفي من الأكسجين والجلوكوز فإن الضرر يعتمد على طول الفترة الزمنية التي تُحرم فيها خلايا الدماغ من الدم على سبيل المثال، إذا كانت خلايا الدماغ الحرمان من الدم لفترة قصيرة فقط يمكن أن تتضرر بشكل طفيف، ولكن إذا حُرمت خلايا المخ من الدم لفترة أطول فقد تموت الخلايا وبالتالي يفقد المريض بعض وظائف الجسم وأحيانًا بشكل دائم. تم تعريف ارتفاع ضغط الدم على أنه عامل الخطر الرئيسي للسكتات الدماغية وهناك عوامل أخرى مثل التدخين، وارتفاع نسبة الكوليسترول في الدم، والسمنة، والرجفان الأذيني، والسكري، وغيرها. تعتبر السكتات الدماغية أكثر شيوعًا بين كبار السن مقارنةً بالبالغين الأصغر سنًا بسبب مخاطر الإصابات التي تؤدي إلى التسبب في السكتات الدماغية مع تقدم العمر. أشارت الإحصائيات إلى أن أكثر من ثلثي السكتات الدماغية تحدث للأشخاص الذين تزيد أعمارهم عن 65 عامًا، في حين أن معدلات السكتات الدماغية عند الرجال أعلى بقليل جدًا من النساء، ولكن أكثر من 60% من وفيات السكتات الدماغية تحدث عند النساء وقد يكون هذا بسبب النساء يصبن بسكتة دماغية في عمر (متوسط) أعلى قليلًا من الرجال. الأشخاص السود لديهم احتمالية أكبر للإصابة بسكتة دماغية مقارنةً بالأشخاص البيض.

الكلمات المفتاحية: السكتة الدماغية، السكتة الدماغية الإقفارية، السكتة الدماغية النزفية وعوامل الخطر الوراثية.