Stroke and Etiopathogenesis

Subjects: Neurosciences

Contributor: Tiziana Ciarambino, Pietro Crispino, Erika Mastrolorenzo, Antonello Viceconti, Mauro Giordano

Stroke is defined as a lack of blood flow in the brain that can cause neurological deficits. The major cause of ischemic stroke is arterial atherosclerosis. Other cause of stroke is genetic etiology and about 15% of strokes are observed in people aged 18–49 years old. Monogenic and polygenic disorders represent about 7% and 38%, respectively, of all stroke causes.

Keywords: stroke ; causes ; etiopathogenesis ; genetic ; epigenetic ; ischemic stroke

1. Association between Genetic Alterations and Risk Factors

Based on linkage analysis, a better understanding was gained for the inheritance of stroke only for those forms of ischemia linked to monogenic disorders. However, it is known that the genetic causes of stroke are also polygenic.

1.1. Monogenic Alterations

Monogenic alterations are responsible for about 1% of strokes those in the young population. Other studies reported that they are responsible for 7% of strokes [1][2][3][4][5][6][7][8][9][10][11][12][13]. Researchers reported the main forms of monogenic stroke:

A. CADASIL—It is an autosomal-dominant arteriopathy characterized by subcortical infarct and leuko-encephalopathy (CADASIL). It is a major monogenic cause of ischemic stroke [14] and it is related to a pathogenic variant of the NOTCH3 gene [15][16] that is inherited in an autosomal-dominant way. The characteristic of CADASIL is deposition of granular osmiophilic material (GOM) in the vascular wall [17].

B. CARASIL—It is an autosomal-recessive cerebral artery disease, and it is related to a mutation of the HTRA1 gene [18]. It is defined by intense arteriosclerosis without amyloid deposits and intimal proliferation or loss of smooth muscle cells in small arteries [19]. Retinal vasculopathy with systemic manifestations (RVCL-S) affects the small vessels of the retina, brain, kidneys and liver and it has an autosomal-dominant inheritance pattern [20]. The gene responsible for RVCL-S is TREX1 and it encodes the TREX1 protein, which, after mutation, makes endothelial cells more vulnerable to oxidative DNA damage [21]. TREX1 is detectable in the microglia surrounding the white matter micro vascularization, and probably the incorrect localization of TREX1 may induce the vulnerability to white matter failure [22][23]. It has been reported that these circulating endothelial markers are present in retinal vasculopathy with cerebral leukoencephalopathy [24][25].

C. MELAS—It is a mitochondrial encephalomyopathy characterized by lactic acidosis and stroke-like episodes (MELAS). The genetic alterations typical of this disease involve the bioenergetic functions of the cell [26]. MELAS is associated with:

- growth retardation
- lactic acidosis
- neuromyopathy
- epilepsy
- migraine-like headache
- recurrent stroke-like episodes (SLE) such as ischemic stroke [27][28][29][30]. Recent data [27][28][29][30] indicate that neuronal and/or glial damage is caused by cerebrovascular angiopathy. In this condition, symmetrical calcifications

in the basal ganglia are reported [27][28][29][30].

D. Sickle cell anemia—It is caused by a point mutation (GAG to GTG) in the ß-globin gene [31]. The clinical manifestations are characterized by chronic hemolysis and acute vaso-occlusive crisis. The prevalence of stroke is about 3.75%, specifically in the first decade of life [32]. Large-vessel occlusion and high development of aneurysms are reported [33][34][35][36].

E. Type IV Ehlers–Danlos syndrome (EDS-IV)—It is a hereditary disorder associated with an abnormal synthesis of procollagen III. It is characterized by heterozygous mutations in the COL3A1 gene [37], and EDS-IV is characterized by facial malformations, skin changes, a tendency to develop bruises and hematomas, and arterial, digestive, and obstetric complications. In this condition, intracranial aneurysms, dissection of the vertebral and carotid arteries and spontaneous rupture of large and medium-sized arteries are reported [38][39].

F. Homocystinuria—It is an autosomal-recessive disease affecting the metabolism of the amino acid methionine. Prevalence has been estimated at 1 in 344,000 [40]. It is characterized by an abnormal accumulation of homocysteine and its metabolites in the blood and urine. Clinical manifestations are heterogeneous and include abnormalities of the eye, skeleton, and nervous system. The complications are related to endothelial damage and the stimulation of platelet aggregation [41].

G. Elastic pseudoxanthoma—It is known as Groenblad–Strandberg syndrome, and it is an autosomal-recessive elastic tissue disease caused by mutations in the ABCC6 gene [42]. Cardiovascular conditions are prevalent in females, and in affected subjects there is an accelerated arteriosclerosis mainly affecting small and medium-sized arteries [43].

H. Fabry disease—It is X-linked recessive and caused by a mutation in the GLA gene encoding the enzyme alpha-galactosidase A [44][45]. Neurological manifestations include polyneuropathy, autonomic dysfunction, and brain manifestations. Stroke may be the first manifestation of the disease, which more frequently affects the posterior cerebral circulation.

I. Marfan syndrome—It is an autosomal dominant condition of the connective tissue, associated with mutations in the fibrillin-1 gene. The incidence is estimated at 2–3/10,000. The clinical characteristics include cardiovascular, skeletal, and ocular symptoms [46][47].

L. Type IV collagen dysfunctions α1 and α2—Both are autosomal dominant conditions, caused by mutations in the COL4A1 (13q34) and COL4A2 (13q34) genes. The clinical features include neurological features (such as stroke, migraine, infantile hemiparesis, epilepsy) and systemic symptoms [48]. Forms of COL4A1 mutations include infantile hemiparesis, seizures, migraine with aura, single or recurrent intracerebral hemorrhages, eye symptoms and muscle spasms [48].

M. Cerebral cavernous malformations—These are known as cavernous angiomas or cavernomas. The prevalence is 0.8% in the general population. The familial form is autosomal dominant and associated with KRIT1 mutations. The clinical manifestations are characterized by seizures, headaches, and intracranial hemorrhage [49]. Cavernous brain malformations can be familiar or sporadic [50].

N. Cerebral amyloid angiopathy—It is responsible for 15% of hemorrhagic strokes. The hereditary form is rare. The degenerative process leads to the development of microaneurysms as well as to hemorrhagic and ischemic lesions of the brain [51].

1.2. Polygenic Cerebrovascular Diseases

Polygenic cerebrovascular diseases are caused by multiple genes. It has been reported that he 38% of variability observed for the thickness of the common carotid artery is attributed to genetic background [52]. Different studies [6][53][54][55] highlight the crucial characteristics of stroke genomics:

- The largest genetic correlation was found for arterial hypertension.
- This suggests a strong link with a cardiac mechanism.
- New stroke risk can constitute drug targets for antithrombotic therapy.

Different risk scores for stroke outcome are described in the literature, such as the Genetic Risk Score (GRS) and the Extended Polygenic Scores (PRS) [56][57]. Different classifications are reported in relation to genetic risk factors, and

previous studies have identified 10 loci associated with stroke [57].

2. Atherosclerotic Stroke

It has been reported that 38% of the variability observed for the thickness of the common carotid artery is attributed to genetic background [9].

2.1. Atherosclerotic Stroke

Ischemic lesions of small diameter (<5 mm), often multiple, with localization in the distribution territory of the arterioles penetrating the basal ganglia, pons, internal capsule, and white matter are called micro lacunar strokes. These strokes are early onset. There are two subtypes of lacunar stroke:

- isolated lacunar stroke.
- multiple lacunar stroke with leuko-araiosis.

Beyond the risk factors, numerous studies have revealed several genetic mechanisms that increase the risk of lacunar stroke [11][13][58][59][60][61]:

- altered oxidative phosphorylation pathways.
- various single nucleotide polymorphisms.

A genetic polymorphism was found at the level of a locus on the chromosome located on the long arm of chromosome 6 (6p25) [62]. Proteins encoded by the FOXF2 gene play a crucial role in DNA repair, cell proliferation and organ development. The associations of this locus with the expression of ZCCHC14 and DNA methylation suggest that together they contribute to the etiopathogenesis of stroke by altering the function of the regulatory elements of cell proliferation [63][64]. Other authors have found several microlacunar stroke–related polymorphisms involving the TRIM65 and TRIM47 genes encoding ubiquitin-like proteins capable of regulating a range of intracellular events [65]. Since these are mainly early-onset strokes, the same study showed that higher blood pressure levels were found in subjects with polymorphisms of these genes, while the polymorphisms of other genes, CSN3, HLA-DPB1 and SH3TC1, are associated with cardiovascular diseases and diabetes mellitus [66][67].

2.2. Cardioembolic Stroke

So far, no genes have been detected that significantly link atrial fibrillation to stroke. However, in ischemic stroke, two genes (PITX2 and ZFHX3), located in the short arms of chromosomes 4 (4q25) and 16 (16q22), respectively, have been reported as significant risk factors for stroke [5][60]. The PITX2 gene encodes a protein that regulates the expression of the procollagen lysyl hydroxylase gene, which is required for the production and stabilization of vessel-supporting collagen. The ZFHX3 gene encodes a protein that regulates myogenic and neuronal differentiation. A single-nucleotide polymorphism in the PITX2 and ZFHX3 genes and two other significantly associated genes, ZNF566 and PDZK1IP1, increase the risk of stroke [12][61].

3. Epigenetic Causes of Stroke

3.1. DNA Methylation

Epigenetic modifications, unlike gene sequence changes, are reversible [68][69]. DNA methylation modulates the interaction between transcription factors with their specific binding sites [70][71]. Pharmacological inhibition of DNA methyltransferase (DNMT) has been shown to decrease the methylation of DNA and to reduce ischemic brain damage in the rat model with middle cerebral artery occlusion [71]. DNA hypermethylation is now associated with many pathogenetic mechanisms involved in ischemic brain damage, reported as follows:

- Hypermethylation of the genetic sequences encoding thrombospondin has been observed in vitro as a cause of ischemia. This factor is involved in platelet aggregation as well as in the neo-angiogenesis, for example, linked to post ischemic damage [71].
- Elevated levels of both triglycerides and low-density lipoprotein (LDL) cholesterol are associated with an increased risk of stroke [72][73][74][75][76]. This phenomenon is correlated in the human organism with the role of apolipoprotein E, a

lipoprotein involved in lipid metabolism [77]. It has been observed that polymorphisms of the ApoE gene, the protagonist of the expression of this lipoprotein, are correlated with a greater progress of atherosclerosis [77]. ApoE hypermethylation can be prevented by reducing homocysteine levels [78].

- In humans, it is also known that high plasma homocysteine levels are an independent risk factor for atherosclerosis and coronary heart disease [79][80][81]. Homocysteine is an amino acid present in the body in very small quantities; it derives from biochemical reactions that start from methionine, an amino acid that we ingest by consuming foods such as meat, eggs, legumes, and dairy products. Alterations in homocysteine metabolism are associated with a higher incidence of stroke. Homocysteine metabolism is regulated by dietary factors such as methionine, B vitamins, methylenetetrahydrofolate reductase (MTHFR), cystathionine beta-synthase (CBS) and methionine synthase (MS). Above all, the hypermethylation of CBS leads to low enzymatic activity and, therefore, the accumulation of plasma homocysteine [81]. High levels of plasma homocysteine are also associated with DNA hypermethylation of thrombomodulin in patients with ischemic stroke [80][81][82].

- The DNA hypermethylation process also seems to be at the basis of the malfunction of the cyclin-dependent kinase inhibitor 2B, a gene involved in the pathogenesis of calcium deposition in the arterial wall [80][81][82].

- Baccarelli et al. [82] reported that hypomethylation of long nucleotide elements was associated with increased levels of a vascular cell adhesion protein (VCAM-1). The association between hypomethylation and the expression of VCAM-1 may be a link for cardiovascular and cerebrovascular diseases [83][84]. In discussing the role of epigenetic factors involving inflammation on the pathogenesis of ischemic injury, it should be remembered that the hypomethylation of TNF receptor–associated factor 3 (TRAF3) and protein phosphatase 1A (PPM1A) was associated with increased risk for stroke in patients treated with antiplatelet therapy [85][86].

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