Literature review

Familial Aggregation of Stroke

P.N. Mukomena[1], S. Lakhi[1], M.H. Mwaba[2], M. Atadzhanov[3]

Department of Internal Medicine, University Teaching Hospital[1], University of Zambia, Promise PEP,[2] Department of Internal Medicine, University of Zambia[3]

INTRODUCTION

Stroke, a focal neurological deficit of sudden onset, is a heterogeneous condition made up of three pathological types: cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage. Cerebral infarction is then further divided into various subtypes, such as intracranial small vessel disease, large-vessel atherosclerotic disease, and embolism from the heart.[1]

Stroke is the second leading cause of death worldwide, and the leading cause of acquired disability in adults in most regions. Fifteen million people worldwide suffer a stroke each year with devastating effects; one third of these individuals die and another one third remains permanently disabled. However, there is a considerable additional unreported asymptomatic cerebrovascular disease. According to the literature, MRI-defined silent brain infarcts can be detected in 20% of healthy elderly people and up to up to 50% of patients in selected series.[1-3]

The burden of stroke is globally increasing and in countries such as the United States of America, there are about 795,000 new and recurrent strokes per year compared with 1,350,000 new and recurrent coronary events. In the west, about 85% of strokes are due to ischemic stroke, and about 15% are due to hemorrhagic stroke, however studies in Africa found higher incidence of intracerebral hemorrhages at 35%.[1,3-5]

Strokes cluster in families and family history of stroke is regarded by both clinicians and the lay public as one of important risk factor for the development of cerebrovascular disease. Nevertheless, data on the genetic epidemiology of stroke remains conflicting.[6]

The purpose of this article is to review studies on familial aggregation of strokes. We searched for studies of family history of stroke and twin studies using bibliographic databases and by hand-searching reference lists and journals. For better analysis of literature, we report separately ischemic and hemorrhagic strokes, and subarachnoid hemorrage.

Ischemic stroke

Ischemic stroke is a complex disorder caused by a combination of genetic and environmental factors. It clusters in families and can be the presenting feature of a number of single-gene disorders, but much more common is the sporadic multifactorial form of this disease. Clinical and epidemiological studies have provided evidence for genetic influences in the development of stroke.[6,7] A number of mendelian traits featuring stroke have been described. The late onset of the non-mendelian, common ischemic stroke and the mode of inheritance, which is complex, polygenic and multifactorial makes it difficult to follow up families with this disorder. In addition, ischaemic stroke consists of a number of different phenotypes which might each have different genetic profiles and run in families.[7,8] We will discuss separately familial aggregation in single-gene disorder associated with ischemic stroke and then in the polygenic, more frequent, multifactorial ischemic stroke.

Familial aggregation in monogenic disorders associated with Ischemic stroke

Familial aggregation, the increased risk of disease among family members compared to the general population, can be attributable to both shared environmental and genetic exposures. Many rare mendelian traits occurring from a single-gene defect have been illustrated in which stroke is a recognized component. Several monogenic disorders can cause large-artery and small-vessel stroke. Generally these represent a small percentage of strokes and will be mostly considered if stroke occurs in young patients with little or no exposure to conventional vascular risk factors.[9,10] The mechanisms by which these disorders result in stroke are diverse and include large arterial disease, small vessel disease, cardioembolism, mitochondrial disorders and connective tissue disorders leading to arterial dissection. However, some familial conditions predispose to stroke by more than one mechanism. We will discuss separately familial

aggregation in large artery, small vessel and cardioembolic diseases.

Large artery disease

These patients will have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis. Clinical findings include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem or cerebellar dysfunction. Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on CT or MRI are considered to be of potential large-artery atherosclerotic origin.[1,11] This stroke can run in families with single-gene disorders including homocysteinuria, dyslipidaemias and sickle cell disease.

Homocysteinuria is an inherited disorder that affects the metabolism of methionine. It is inherited in families as an autosomal recessive trait and causes stroke by thromboembolic vascular events. Several autosomal dominant and recessive enzyme deficiencies exist which can lead to a high level of homocysteine in both plasma and urine, and this condition is referred to as homocysteinuria. Homocysteine is believed to be toxic to endothelial cells and to predispose to a prothrombotic state, and it is associated with premature atherosclerosis.[12] According to one study, one-half of the patients with inherited cystathione β-synthase deficiency suffered from a thromboembolic episode before the age of 29 years, and in 32% of these cases this was a cerebrovascular event.[13] Treatments to lower plasma homocysteine levels and stroke risk include pyridoxine, methionine-restricted diet, folate and vitamin B12 supplementation, and betaine.

Several studies have suggested that mild to moderate elevations of serum homocysteine are associated with increased risk of vascular disease. Homocysteine levels tend to be higher in individuals homozygous for the thermolabile variant of the methylene tetrahydrofolate reductase (***MTHFR)*** gene, due to a C-to-T transition at position 677. Studies found an increased risk of atherothrombotic stroke in carriers of the TT genotype of the 677C_T variant in ***MTHFR.*** [14,15]

Hereditary dyslipidaemias linked with premature atherosclerosis may lead to early stroke. Elevations of LDL cholesterol can result from single gene defects or be associated with polygenic disorders or secondary to other diseases. Familial hypercholesterolemia is due to mutations in the gene for the LDL receptor. Familial Defective Apo B100, an autosomal dominant disorder, is due to a missense mutation at aminoacid 3500 that reduces the affinity of LDL for the LDL receptor thus impairs LDL catabolism.[16] The association between these disorders and ischemic stroke is less well described than that with coronary artery disease, but a relation has been reported in several disorders, including familial hypoalphalipoproteinaemia, familial hypercholesterolaemia (homozygous form), type II and type IV hyperlipidemia and Tangier's disease.[17]

Sickle cell disease may cause cerebral infarction via both arterial involvement and a prothrombotic predisposition. Stroke, an important complication of sickle cell disease**,** affects around 8% of children with homozygous sickle cell disease in the first 14 years of life and up to 25% in patients aged 45 years and above including both large-artery and small-vessel ischemic stroke and hemorrhagic stroke.[18] Large-artery strokes are due to intimal thickening, fibroblast and smooth muscle cell proliferation, and thrombus formation, mainly in the distal internal carotid artery and the proximal middle and anterior cerebral arteries. Small-vessel strokes are probably caused by sludging and intravascular sickling in smaller vessels. Transfusion therapy can reduce the risk of stroke.[19,20]

A prothrombotic state resulting from a deficiency of protein C and protein S is a well documented cause of familial venous thrombosis. The association with arterial stroke is less strong. Reduced levels of proteins C and S may occur transiently after stroke, while low levels may be seen in patients on warfarin therapy and in conditions such as liver disease, disseminated intravascular coagulation and renal disease.[21]But in the presence of a family history of premature thrombosis, the association is likely to be causal. In elderly individuals, the relationship between the levels of these natural anticoagulants and stroke appears to be weak. Furthermore, the risk of venous thrombosis is much higher than that of arterial thrombosis hence the likelihood of a patent foramen ovale leading to a right-to-left cardiac shunt should therefore be considered in patients with stroke (paradoxical embolism). Antithrombin III deficiency, inherited as an autosomal dominant trait, is also largely associated with venous thrombosis but uncommon cases of arterial stroke have been reported.[21,22,23]

Small vessel disease

In this category we include patients whose strokes are often labelled as lacunar infarcts. The patient should have one of the traditional clinical lacunar syndromes and

should not have evidence of cerebral cortical dysfunction. A history of diabetes mellitus or hypertension supports the clinical diagnosis. The patient should also have a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm demonstrated. Small vessel disease is a pathological term used to refer to the structural changes affecting the small penetrating end arterioles which supply the deep white matter and basal ganglia.[11] Lacunar strokes can run in families with single gene defect such as CADASIL or Fabry's disease.

CADASIL, Cerebral Autosomal Dominant Arteriopathy, Subcortical Infarcts and Leukoencephalopathy, is a rare autosomal dominant disease caused by mutations in the *Notch3* gene on chromosome 19. The clinical phenotype is characterized by familial syndrome of recurrent subcortical stroke-like episodes, which occur commonly in mid-adulthood in the absence of usual vascular risk factors.[24]The underlying vascular lesion is a non arteriosclerotic, amyloid-negative angiopathy involving small arteries and capillaries. Since these changes have been reported in the small vessels supplying the peripheral nerves, skin, muscle, and occasionally the viscera, indicating the presence of systemic arteriopathy, skin biopsy has been used in the diagnosis. MRI reveals leucoencephalopathy and small deep infarcts (leucoariosis) in all symptomatic patients, both focal lacunar infarcts and diffuse leucoariosis are seen on T_2-weighted images. In patients with a characteristic phenotype and family history, the approach to screening is to initially look for mutations in exons 3 and 4, and also to consider a skin biopsy. Though it is diagnostic if granular osmiophilic material is present, the skin biopsy can be normal.[24,25]

Fabry's disease is an X-linked recessive disorder due to α-galactosidase A deficiency, stroke occurs most frequently from the third decade onwards. Progressive changes within the intima and media of blood vessels results in luminal narrowing and complications such as stroke and myocardial ischaemia. Stroke may occur secondarily to large vessel disease, small vessel disease, or embolism from associated cardiac disease. Involvement of large vessels appears to affect the vertebrobasilar system preferentially, and therefore ischaemia is most common in this territory.[18,26]

MELAS, Mitochondrial Encephalomyelopathy, Lactic Acidosis and Stroke-like episodes, is a mitochondrial encephalopathy that is characterized by seizures, stroke-like episodes, migraine-like headaches, nausea, vomiting, lactic acidosis, ophthalmoplegia, ptosis, sensorineural hearing loss and dementia. It is caused by mutations in the mitochondrial DNA, which are transmitted maternally. Muscle biopsy usually reveals abnormal mitochondria and ragged red fibres.[18,27]

Arterial dissection could rarely be the consequence of an underlying heritable connective tissue disease resulting in ischaemic stroke. Defects in collagen synthesis can predispose individuals to spontaneous dissection of the extracranial carotid and vertebral arteries in Ehlers–Danlos syndrome type IV while in Marfan syndrome the common neurovascular complication is extension of an aortic dissection into the common carotid artery and there are isolated case reports of vertebral dissection in osteogenesis imperfect.[18]

Cardioembolic stroke

This category includes patients with arterial occlusions presumably due to an embolus arising in the heart. At least one cardiac source for an embolus must be identified for a possible or probable diagnosis of cardioembolic stroke.[11]This stroke can run in families with single-gene disorders including hereditary cardiac conduction defects, inherited cardiomyopathies and familial atrial myxomas. Cardiomyopathies may present as a primary cardiac disorder (e.g. hypertrophic obstructive cardiomyopathy) or be secondary to a neuromuscular disorder (e.g. Duchenne muscular dystrophy) or one of the inborn errors of metabolism (e.g. Menkes disease, an X-linked neurodegenerative disease). Idiopathic autosomal dominant mitral valve prolapse may confer a little risk of cardioembolic stroke but patients with forms of autosomal dominant or recessive dysrhythmias and familial atrial myxoma may be at very high risk.[28,29]

Familial aggregegation in polygenic multifactorial ischaemic stroke

Apart from rare monogenic disorders associated with stroke, ischemic stroke is a complex polygenic and multifactorial disorder caused by a combination of genetic and environmental factors.[18]Animal studies suggest that genetic factors may play a role in the susceptibility to infarction during cerebral ischemia.[30]There is evidence in the literature, both from twin studies and from studies on the family history of stroke that genetic factors substantially contribute to stroke susceptibility.[31] However, the influence of family history on stroke risk remains controversial, with some studies describing no impact of parental history on stroke risk.[32]The modulatory effect of genes on the extent and

pattern of end-organ damage resulting from conventional risk factors may be particularly important. For example, certain hypertensive individuals develop cerebral small vessel disease without any evidence of large vessel atherosclerosis, while in others the opposite occurs, or a combination of the two patterns may be present. The reasons for these different patterns are unknown but genetic factors may determine whether hypertensive individuals develop other manifestations of end-organ damage, such as cardiac left ventricular hypertrophy.[33]

For each stroke subtypes, genetic factors may act either by predisposing to conventional risk factors such as hypertension, by modulating the effects of such conventional risk factors on the end organs, or by a direct independent effect on stroke risk. The well known conventional risk factors, such as hypertension, hyperlipidemia and diabetes are themselves believed to be under genetic control and run in families; twin and sibling studies have also shown that these intermediate phenotypes for stroke are under strong genetic control.[31,34]

Epidemiological studies have used twin, affected sibling pair and family based approaches to investigate familial aggregation of stroke.

Using twin studies, Brass et al[31] found a stroke concordance rate of 17.7% in monozygotic twins as opposed to 3.6% in dizygotic twins, giving a relative risk of 4.3. However, it was not possible to calculate the heritability of stroke in this study as only a few twin pairs were studied. Later (after a decade), this cohort was reassessed and genetic influences was found to have little influence on the risk of stroke in the older population, in whom much of the variance was accounted for by environmental exposure. This is consistent with the role of genetic stroke risk factors being strongest in younger adults.[35]

In another study, the heritability of common carotid artery intimal medial thickness was found to be 92%. Of interest, the role of genetic factors was not through usual risk factors used as covariates in the analysis. However, this study was performed in siblings rather than twins, making it not easy to account for the role of early shared environmental effects and genetic influences.[36]

Family based studies have examined the relationship between a family history of stroke amongst first-degree relatives and risk of stroke in probands. Whilst a positive family history is consistent with the role of genetic factors, alternative but not exclusive explanations, such as shared environmental influences, could be valid. With this in mind, the results of several large studies are consistent with a family history of stroke being an important independent risk factor.[37]

In the original Framingham cohort it was reported that a parental history of stroke did not confer an increase in the risk of stroke but amongst the progeny cohort there was an association with parental stroke history. The presence of an atherothrombotic brain infarction in a sibling also conferred a relative risk of 1.8.[38]

The importance of parental history was also seen in a prospective follow-up of a Finnish population, in which a positive parental history of stroke led to a two fold increase in stroke in both men and women. The association between family and personal history of stroke appeared to be stronger in younger stroke patients.[35,39]This was also found in a cross-sectional study, in which younger stroke victims were more likely to have an offspring who had a fatal coronary or cerebrovascular event. A positive stroke history was recorded in 47% of patients, compared with 24% in the study by Graffagnino et al.[40] However, the difference was no longer significant after controlling for conventional risk factors. Furthermore, as hypertension and diabetes are known to have a strong genetic component, clustering of these risk factors within families may partly account for the familial aggregation of stroke. This has been suggested by the study by Diaz and colleagues, in which it was found that siblings of patients with cerebral infarction or transient ischaemic attack were more likely to have multiple vascular risk factors than the siblings of spouse controls.[41]There have also been some notable negative studies. However, most studies suggest that a family history of stroke is an independent risk factor for stroke, and this is consistent with a genetic component operating outside the usual risk factors. In one study it was reported that a maternal history of stroke was associated with a threefold increase in stroke in a cohort of men.[42] This is at odds with results from the Family Heart Study and the Framingham cohort, in which it was found that individuals with a paternal history of stroke were more likely to have a stroke than those with a maternal history, which conferred a slightly lower risk.[38] Interestingly, in the Rancho Barnardo study, a family history of stroke in any first-degree relative at baseline was an independent predictor of stroke mortality in women but not in men, which suggests a sex-specific interaction for the genetic risk of stroke.[43]

Most cases of ischemic stroke represent a multifactorial, polygenic disorder or complex trait for which typical

model of inheritance cannot be established. Therefore, familial aggregation of this multifactorial stroke may be related to one or more of the following disorders of: (i) haemostasis, (ii) the renin–angiotensin system, (iii) nitric oxide production, (iv) homocysteine and (v) lipid metabolism.

Renin-Angiotensin System

The angiotensin-converting enzyme (*ACE*) gene (insertion or deletion polymorphism in intron 16) is one of the most commonly studied genetic variations in relation to atherosclerosis and vascular disease (coronary and cerebrovascular). ACE regulates vascular tone by converting angiotensin I to the vasoconstrictor angiotensin II inactivating the vasodilator bradykinin, hence contributing to the regulation of vascular tone, endothelial function, and smooth muscle cell proliferation. The insertion/deletion polymorphism in the *ACE* gene was significantly associated with lacunar stroke with an increased risk for D-allele carriers.[44] A meta-analysis has evaluated the risk of stroke in 1918 subjects versus 722 controls from seven studies. It was concluded that the ACE genotype conferred a small but modest effect, with an odds ratio of 1.31 (95% confidence interval 1.06–1.62), according to a dominant model of inheritance. A number of studies have reported an association that was strongest or exclusively with lacunar stroke.[45,46]

Thrombosis and Hemostasis

The role of platelet glycoprotein receptor polymorphism has also been studied extensively in patients with ischaemic stroke. Platelet glycoprotein receptors when activated, bind fibrinogen, von Willebrand factor, or collagen, and hence promote platelet aggregation and thrombosis. An increased risk of atherothrombotic stroke was found in A2-allele carriers of the integrin3 (*ITGB3* or *GPIIIa*) P1(A1/A2) variant (rs5918) in different studies.[47,48]

Factor XIII catalyzes the formation of covalent bounds between fibrin monomers, which stabilizes the fibrin clot, and is also involved in the cross-linking of 2 antiplasmin, fibronectin, and collagen. Studies also found an increased risk of atherothrombotic stroke associated with the Val/Val genotype of rs5985 in *F13A1* (coagulation factor XIII, A1 polypeptide), but other studies found no association. A polymorphism in the factor XIII gene (Val 34 Leu) has also been examined in ischaemic stroke after reports that this polymorphism was protective in myocardial infarction.[49,50]

Inflammatory System

Inflammation is a key process in atherosclerosis and therefore stroke and coronary heart disease. Leukotrienes are potent proinflammatory molecules. One genetic variant in the leukotriene C4 synthase (*LTC4S*) gene was found to be associated with lacunar stroke in 2 different populations, with an increased risk for A-allele carriers.[51] Interleukin (IL)-6 inhibits the production of potent proinflammatory cytokines, such as tumor necrosis factor-and IL-1. Increased levels of IL-6 in the plasma and cerebrospinal fluid were shown to correlate with infarct size and functional outcome of patients with stroke. A genetic variant in the *IL-6* gene was associated with lacunar stroke in 2 different populations, with an increased risk for CC-homozygotes. Raised fibrinogen levels may predispose to stroke both by accelerated atherosclerosis and prothrombotic mechanisms.[51-53]

Lipid Metabolism

Individuals with increased plasma cholesterol, especially low-density lipoprotein, levels are at a higher risk of premature atherosclerosis. Thus, genes encoding proteins involved in plasma lipoprotein metabolism are interesting candidates when looking for genetic risk factors of ischemic stroke.[54] The phenotype may arise not only from single gene disorders, as discussed above, but also from a number of genetic and environmental factors, including polymorphic variants of genes encoding the apolipoproteins, lipoprotein receptors and the key enzymes of plasma lipoprotein metabolism. Apolipoprotein E (**ApoE**), a glycoprotein mainly synthesized in hepatocytes, mediates the binding of lipid particles to specific lipoprotein receptors and there are three major alleles of ApoE gene encode E2, E3 and E4. Individuals who are homozygous for Apo E2 may develop severe hyperlipidemia (type III dyslipoproteinemias), and complete absence of Apo E causes elevations of plasma levels of chylomychrons and VLDL remnants and early arthrosclerosis. The E4 variant has been associated with higher total serum cholesterol and LDL cholesterol levels, and has been postulated as an important risk factor in ischaemic stroke. An increased risk of atherothrombotic stroke was found for *APOE* 4 carriers in different studies.[55,56,57]

Endothelial Function and Oxidative Stress

It is known that homocysteine levels tend to be higher in individuals homozygous for the ***MTHFR*** gene, due to a C-to-T transition at position 677 with increased risk of atherothrombotic stroke in carriers of the TT genotype.[14]

The activity of the L-arginine/nitric oxide synthase system is an important mediator of endothelial function. It has diverse effects, including the regulation of the tone, integrity, growth and thrombogenic properties of the vessel wall.[58] Strong evidence from animal and human studies indicates that the activity of this system is under genetic control.[30,59] Work in the stroke-prone Spontaneously Hypertensive Rat (SHR) has suggested that impaired endothelial function is an important predisposing factor leading to stroke. In addition, knockout mice deficient in endothelial nitric oxide synthase are highly sensitive to focal cerebral ischaemia and have marked vessel wall abnormalities.[60,61]The genes encoding nitric oxide synthase are potential candidate genes for stroke. In animal models, their inhibition reduces infarct size, which is also smaller in knockout mice. Both genes have been cloned and common polymorphisms described.

Intracerebral hemorrhage (ICH)

ICH is commonly classified according to the region of the brain in which it occurs—the thalamus, basal ganglia, brain stem, and cerebellum ("nonlobar"), or at the junction of the cortical gray matter and subcortical white matter ("lobar"). It occurs sporadically or as part of familial syndromes. As a complex disease, ICH aggregates in families but does not segregate in a mendelian fashion. Genes reported as associated with ICH are involved in the pathways of the vessel wall integrity (*ACE, APOE, endoglin, TGF-β1*), endothelial dysfunction (*ACE*), haemostasis (*APOE, CD-14, Factors VII and XIII*) and inflammation markers (*IL-6, TNF*).[62,63]

Woo D et al. reported that history of ICH in a first-degree relative increases a subject's odds by as much as 2 to 6 fold and significant independent risk factors for lobar ICH included the presence of an apolipoprotein E2 or E4 allele, frequent alcohol use, prior stroke, and first-degree relative with ICH. For nonlobar ICH significant independent risk factors included hypertension, prior stroke, and first-degree relative with ICH.[64]

Although ICH can result from rupture of vascular malformations and saccular aneurysms, the overwhelming majority of ICH in the elderly occurs as a manifestation of **cerebral small vessel disease**. Lobar ICH accounts for 25% to 35% of ICH depending on the population studied. Pathological studies demonstrate that the location of ICH in the elderly frequently signals different underlying small vessel diseases. For example, whereas chronic hypertension has long been recognized as a leading cause of ICH, the majority of ICH in lobar brain regions may be unrelated to hypertensive vasculopathy, arising instead from cerebral amyloid angiopathy (CAA).[24,25,65]

Other risk factors are shared by both lobar and nonlobar ICH. For example, alcohol exposure appears to predispose to both lobar and nonlobar ICH. Data on familial aggregation point to a strong familial contribution to ICH, both lobar and nonlobar. The small vessel pathologies responsible for ICH can also cause other forms of brain injury. These are microbleeds, visible on MRI as dot-like susceptibility artifact and leukoaraiosis.

Leukoaraiosis is extremely common in the aging population and is strongly heritable. Studies demonstrate substantial heritability across multiple populations. Among 74 monozygotic and 71 dizygotic male American male twin pairs age 68 to 79 at time of MRI, heritability of was 0.71 (95% CI 0.66 to 0.76).[25]

Microbleeds, but not ICH, commonly occur in CADASIL, the hallmark on neuroimaging is diffuse leukoaraiosis on MRI with particular involvement of bilateral anterior temporal lobes and external capsule, as well as presence of microbleeds.[24,25]

Subarachnoid hemorrhage (SAH)

Subarachnoid hemorrhage (SAH) comprises 1% to 7% of all strokes. Despite its relative rarity, it is a public health problem due to the relatively young age of onset and poor outcome.[66]

SAH, in 80%-90% of cases due to rupture of an intracranial aneurysm, occurs at all ages but strikes primarily in middle age, frequently with devastating consequences: around 40% of patients admitted to hospital die within 1 month and more than one third of survivors have severe disability.[67] Several studies have indicated that smoking, hypertension, and alcohol misuse are important risk factors for subarachnoid haemorrhage due to aneurysms. Genetic factors may also have a role as close relatives harbour intracerebral aneurysms more frequently than the background population. Furthermore, intracranial aneurysms have been associated with numerous heritable connective tissue disorders, which account for at least 5% of cases. Of these disorders, the most important are Ehlers-Danlos syndrome Type IV, Marfan's syndrome, neurofibromatosis Type 1, and autosomal dominant polycystic kidney disease; the association with intracranial aneurysms, however, has been firmly established only for polycystic kidney disease. Familial intracranial aneurysms are not rare but

account for 7 to 20% of patients with aneurysmal subarachnoid hemorrhage and are generally not associated with any of the known heritable connective tissue disorders.[68]

Familial studies indicate that first degree relatives (parents, full siblings, and children) are at increased risk of subarachnoid haemorrhage. In most studies, information on pedigrees and identification of cases among relatives are based on self reported or proxy reported data, which can be subject to selection and recall biases making quantitative estimates inaccurate. Population based registries are less likely to be subject to recall bias.[69]

Although familial preponderance suggests a genetic influence, most instances of SAH can be attributed to lifestyle exposures. Hence, identification of modifiable risk factors for SAH is pivotal to reducing its incidence, which appears to have remained relatively stable in many countries over recent decades.[66]

First degree relatives of patients who had a subarachnoid haemorrhage are at an estimated threefold to fivefold increased risk of subarachnoid haemorrhage compared with the general population.

A family history of SAH has been linked with an increased risk for SAH of about 4 fold; for this reason, screening of first-degree relatives of patients with SAH is recommended. Evidence of a gene-environment interaction with smoking, another risk factor for SAH, also may exist for aneurysmal SAH.[70]

Familial cases of intracranial aneurysm have been reported to occur, with a slight preponderance in women, at a younger age, and with similar severity and case fatality as non-familial cases. The pathogenesis of familial intracranial aneurysms is not fully explained; a deficiency of type III collagen has been reported in sporadic, but not in familial, cases.[70]

Some families show a frequency of intracranial aneurysms compatible with an autosomal dominant mode of inheritance. A genetic basis is also suggested by the younger average age of familial cases with a ruptured intracranial aneurysm, occurrence at the same site or a mirror site in sibling pairs, occurrence in identical twins, and the association of intracranial aneurysms with genetically transmitted disorders.[71]

In a case-control study of 149 patients with subarachnoid haemorrhage, cases were 1.8 times more likely than controls to report having first degree relatives with subarachnoid haemorrhage. In another study, 11 first degree relatives of 76 patients with subarachnoid haemorrhage had an aneurysmal subarachnoid haemorrhage, which corresponded to a relative risk of 4.1 compared with the background population. De Braekeleer et al traced 533 cases of subarachnoid haemorrhage and unruptured intracranial aneurysms through hospital registries, and matched controls were identified through a population register in an isolated population with a high degree of inbreeding. Cases were 4.7 times more likely to have affected first degree relatives than were controls. [72,73]

Smoking, hypertension, and excessive alcohol intake have statistically significant and consistent associations with an increased risk of SAH in case-control and longitudinal studies. Because of the increase in the number of studies in this analysis, the estimates of association obtained are more precise. Studies found that the risk of SAH in former smokers is almost twice that of never smokers.[67]

CONCLUSION

Most studies suggest that a family history of stroke is an independent risk factor for stroke and a positive family history of vascular disease is an independent risk factor for both hemorrhagic and ischemic strokes, especially in the young patient without usual cardiovascular risk factors. Although family history of stroke is one of important stroke risk factor, recall bias is among important biases in family history studies.

The importance of the accurate classification of stroke type and subtype in studies needs to be appreciated, as ischemic and hemorrhagic strokes are not under the same genetic influence.Most studies report familial aggregation of all strokes but stroke types and subtypes are not expected to be evenly heritable, and case merge is so prone to influence the findings.

Most familial stroke studies report strong association of stroke between siblings compared with the rather weak association of stroke between spouses suggesting that genetic factors might be stronger predictors of stroke than environmental factors. However, further studies of the human genome are needed in order to identify the specific genes that play roles in the pathogenesis of different types and subtypes of stroke.

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