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Risk Factors of the Development and Rupture of Cerebral Aneurysms

ABSTRACT

Background and purpose. This review examines the evidence of epidemiological, pathophysiological and genetic studies on the search for risk factors of non-traumatic cerebral aneurysms and subarachnoid hemorrhage.

Summary of the review. The epidemiological studies indicate significant differences in the incidence of subarachnoid hemorrhage in different populations. No one of the established risk factors can explain this phenomenon, and thus, likely there are other risk factors affecting the development of the disease. Mechanisms of aneurysm's development and rupture are not sufficiently clear currently. It was established the influence of genetic factors on the development of the cerebral aneurysms in many studies.

Conclusions. The data of recent studies suggest that the development and rupture of cerebral aneurysms are due to a complex interaction of modifiable factors and genetic predisposition. The discovery of new risk factors of the disease, including genetic ones, contributes to the understanding of mechanisms of cerebral aneurysms, and could be the basis for the prevention of subarachnoid hemorrhage.

Keywords: cerebral aneurysm¸subarachnoid hemorrhage, genetics.

INTRODUCTION

Cerebral arterial aneurysm (CA) is a local protrusion of the brain blood vessel's wall and is the most common cause of non-traumatic subarachnoid hemorrhage (SAH). Despite impressive advances in the diagnosis and surgical treatment of ruptured CA occurred recently, SAH is a common disease with a high fatality rate. Mechanisms of development and rupture of the CA are largely unclear currently. The epidemiological, pathophysiological and genetic studies on the search for risk factors of cerebral aneurysms and subarachnoid hemorrhage are examined in the present review.

Epidemiology. The CA incidence is estimated at about 5-10% in a population [15]. Currently, a significant number of CA diagnosed incidentally as a result of surveys conducted in conditions not related to the SAH. This is due to the widespread introduction into clinical practice of such methods of examination as magnetic resonance angiography (MR angiography) and computer tomography angiography (CT angiography, CTA) [56]. For example, the cerebral aneurysms were diagnosed in 1.8% of cases when the MRI examination of 2,000 people was performed (RotterdamStudy) [30].

The CA rupture leads to the development of subarachnoid hemorrhage. Approximately 85% of SAH are caused by rupture of saccular aneurysms in the brain base [2].The low rate of the SAH incidence in the population compared to the CA incidence is probably due to the majority of aneurysms is not broken [15].

SAH has the high mortality rate [2, 10, 11, 27]. It ranged from 8.3% to 66.7% according to the data of 33 population-based studies [10]. Recently, there has been a downward trend in SAH mortality, caused by the improvement of diagnosis and treatment [10]. After SAH the 12% of patients have significant limitations in daily activities (3 points on the modified Rankin scale), another 6.5% of patients are depending on outside assistance (4-5 points on the modified Rankin scale) [10]. Cognitive disorders associated with poor functional recovery and low life quality diagnosed in 20% of patients after SAH [40].

According to a meta-analysis of 51epidemiological studies [28] SAH incidence is approximately 9100000 person-years, but varies widely in different countries. Thus, the incidence in Japan and Finland has almost two-fold average, whereas in Central and South America, by contrast, the incidence is significantly lower (22.7; 19.7and 4.2, respectively)[28].

SAH incidence increases with age [28, 49]. For example, the incidence in age<25 years old was 2, 0100000 person-years; 25-35years –7.7; 35-45 years–0.52; 45-55years–19.5; 55-65years–24.8; 65-75years–25.4; 75-85years–26.2years; >85 years–31.3[28]. The SAH incidence in children is low and increases with age. According to the study [57], the incidence in the teens (15 to19 years) is 0.52per 100 000 person-years; while in the age from 0to 4years–0.06; from 5 to9 years–0.05; from 10 to14 years–0.09.

In addition, the gender-specific SAH prevalence is described: the incidence is higher in the female compared to the male (OR = 1.24 (95% CI: 1.09 -1.42)) [28]. The reasons for the high SAH incidence among the women are unclear, but a possible explanation are hormonal factors (including the use of hormone replacement therapy) [26, 53]. Gender distribution in different age groups are not identical: the incidence is higher in men in the young age (25-45 years), while in women – in age >55 years [28].

The differences in the SAH incidence depended on ethnicity and race are described. For example, the Blacks and Hispanics have a higher SAH incidence compared to the Caucasians [17, 51, 54, 58]. Ethnic features in the hospital hemorrhagic stroke structure, including the SAH, were established in the study [12]. Share of hemorrhagic stroke among the Asian indigenous is higher compared to the Caucasians in Yakutia (OR = 2.42; 95% CI: 1.72-3.41) [12]. The reasons for this phenomenon are currently unclear.

Significant differences in the SAH incidence, depending on the region of the world, are the subject of the many studies. This phenomenon is probably due to genetic causes and diagnostic features of the disease in different countries [21]. Several factors that can cause SAH high levels in Finland and Japan are described, but the extent of their contribution to the development of the disease remains unclear. For example, the high morbidity in Japan could be affected by such factors as the more elderly average age of the population (compared to the other ones) [61]; careful consideration of the sudden pre-hospital death, the cause of which could be SAH; as well as the widespread use of neuroimaging techniques for the diagnosis of hemorrhage [28]. The factors of the high level of SAH morbidity in Finland indicate greater prevalence of smoking, hypertension [50] and alcohol [34]. The low SAH incidence in the South and Central America are likely to be explained by the younger average age of the population [29]; lack of access to medical care in these regions [28], which could affect the quality of diagnosis. Another explanation for the differences in the SAH incidence may be due to the racial characteristics. However, none of the above factors can explain fully the difference in the SAH incidence between regions [28] and thus probably there are other factors affecting this phenomenon.

During the past decades, the SAH incidence decreased (approximately 0.6% per year) [28], while this decreasing is much moremodestthan the reducing dynamics of the stroke incidence in general. The reason for this phenomenon may be that the SAH development is more depending on genetic factors, than a stroke in whole [15].

Pathogenesis. Rare causes of the CA include Ehlers-Danlos syndrome type IV, a hereditary defect in collagen with saccular and fusiform aneurisms [55], and mycotic aneurysm [2]. Autosomal dominant polycystic kidney disease is a risk factor for CA, and it is the cause of less than 1% of non-traumatic SAH. The patients with this disorder have CA in 10-13%, most aneurysms are located in the middle cerebral artery [55]. Other rare risk factors for CA are sickle cell disease, coarctation of the aorta [55].

Most of the CA are not innate and develop over a lifetime. This is confirmed by the fact that aneurysms are very rare in children [28, 57]. The pathogenesis of the vast majority of the CA includes several interacting mechanisms. The thinning of the structural elements of the vascular wall, such as the internal elastic membrane and the extracellular matrix, is considered as the main reasons for the development of CA [1]. The hemodynamic effects, which lead to changes in the internal elastic membrane, followed by thinning of the media and the outward protrusion of the vessel wall, play a key role inthis process [1, 35, 36, 47, 62]. Cerebral aneurysms are most common in places under the strong hemodynamic effects, such as in arterial bifurcations and angulations [22]. Various mathematical models have shown that the bifurcation and angulation areas are experienced the abnormally high hemodynamic stress, which leads to hemodynamic stress and remodeling of the vascular wall [22]. The formation of the aneurysm begins with the endothelial damage, with subsequent the development of inflammation, which leads, in turn, to the tear or defect of the vessel wall. The extension of this vessel defect produces a cerebral aneurysm [14]. Inflammation is a critical process that preceded the formation and rupture of CA [59]. Tumor necrosis factor alpha (TNF-α) is the key immune modulator, which is involved in the pathophysiology of CA [60].

The apoptosis of smooth muscle cells of a cerebral vessel is important in the mechanism of CA [2, 42]. Reducing the number of smooth muscle cells associated with apoptosis may lead to a violation of the elastic fibers synthesis [2]. Matrix metalloproteinase (MMPs) also take part in the extracellular matrix remodeling [25, 33, 45], resulting the loss of internal elastic membrane, medial thinning, and aneurysm formation. The structure of the vascular wall of the ruptured CA and the unruptured CA are different. Ruptured CA are characterized with the considerable infiltration of the aneurysm wall by macrophages, leading to the loss of smooth muscle cells, matrix proteins and rupture of CA [52].

Probably the atherosclerotic process plays an important role in the CA pathogenesis. This assumption is confirmed by the fact that arteriosclerosis is an important element in the development of aneurysms occurring in other vessels, such as aorta [37, 41, 63]. The presence of atherosclerotic vessel wall lesions is CA peculiarity, which occur even in the small size aneurysms, where in the progression of atherosclerotic lesions was positively correlated with the growth of the aneurysm [32]. According to some authors, the atherosclerotic process involved in the formation, growth and subsequent rupture of CA [5, 24, 32], while other ones do not support this hypothesis [19].

To date, there is no consensus about the CA growth dynamics. It is more likely that intracranial aneurysms generally not grow at a constant rate. According to study [20], the real growth process is irregular and intermittent, with periods of stability or periods of growing with the low and high risk of CA rupture, respectively. The study [3] examined the chronology of the CA development by the method of determining the time of occurrence of a radioactive isotope of carbon (14C) in collagentype I, which is a dominant component of the molecular target audience. The samples of the ruptured CA and the unruptured CA of the Asian patients who underwent surgical treatment were studied. It was established that all samples with the age of the aneurysm's formation<5 years contained the collagen type I. This phenomenon was not depended on the patient's age, CA size, morphology, presence of aneurysm rupture. However, the collagen age was significantly lower in patients with a history of risk factors such as smoking or hypertension, compared to patients without risk factors (1.6 ± 1.2 vs. 3.9 ± 3.3years,respectively; $p = 0.012$). Thus, the presence of large amounts of newly formed collagen type I in aneurysm presupposes the existence of constant remodeling of collagen, which is much faster in patients with risk factors [3].

The most important factors affecting the risk of CA rupture are the size and location of the aneurysm [9, 15, 31, 43]. CA rupture risk increases when the aneurysm has a large size (>7 mm) [31]. The risk of rupture of the aneurysm increases when CA localization is front communicating artery [31], according to other authors – in the posterior part of the Willis'circle [43]. Additional risk factors are smoking hypertension, alcohol abuse, family history [31, 44, 46]. Use of skim milk and fruit, on the contrary, reduces the risk of SAH [48]. In addition, the same effect has been demonstrated for dietary antioxidants and soybean products [38, 39].

Genetic factors. The increased risk of aneurysms in relatives of patients with SAH confirmed the genetic component in the CA development [15, 43, 55]. The hereditary aneurysms more frequently localized in the middle cerebral artery, are larger and are often multiple compared to the sporadic aneurysms [15]. Most of the prevalence of CA in patients with polycystic kidney disease, Ehlers-Danlos syndrome type IV and fibromuscular dysplasia also supports the theory of the existence of the genetic mechanisms contribute to the formation and rupture of the aneurysm [55].

The recent large meta-analysis [4] included the research data of the possible associations of 41 single nucleotide polymorphism (SNPs) of 29 genes with the risk of CA, which have been published in electronic databases (PubMed, EMBASE, GoogleScholar) until December 2012. Total analysis summarized the data obtained in the study of 32,887 individuals with CA and 83,683 control subjects, who were unrelated individuals with confirmed (by CT / MRI - angiography and digital subtraction angiography) of the populations of Europe, Japan and China. Cases of intracranial aneurysms with hereditary diseases, such as polycystic kidney disease in adults or Ehlers-Danlos syndrome are not included in the study. Total analysis included the 66 studies, as well as studies of 60 single nucleotide variants of candidate genes and 6 genome-wide studies. The analysis identified 19 SNPs, associated with the CA. The most robust associations were obtained for 11 of the 12 SNPs founded in the genome-wide studies: loci on chromosome 9 (rs1333040 and rs10757278), chromosome 8 (rs9298506 and rs10958409) and chromosome 4 (rs6841581), as well as variants 9p21.3 (rs2891168), 2q33 (rs1429412 and rs700651), 7q13 (rs4628172), 12q22 (rs6538595) and 20p20.1 (rs1132274). 8SNPs were identified in studies of association of candidate gene variants with the CAA risk. The genetic variant *SERPINA3* (rs4934) and 2 variants associated with collagen gene (*COL1A2* [rs42524 G> C] and *COL3A1* [rs1800255 G> A]), showed the most strong association with the disease. Another SNPs gene variants associated with CA included: geparansulfataproteoglikan 2 (rs3767137), versican (rs251124 and rs173686), and angiotensin-converting enzyme (*ACE) I / D* and interleukin 6 (*IL-6*) G572C. The diversity of genes identified in this meta-analysis indicates the existence of multiple pathophysiological mechanisms that contribute to the CA development and rupture. These mechanisms include regulation of the vascular endothelium and extracellular matrix integrity [4].

As a result of the search carried out in the database PubMed (2013 – February2015.), we found several new studies in the possible associations of genetic variants with the CA risk. The study [8] founded the association of *COL1A2* gene polymorphisms with CA risk in the German population. In the study of the possible relationship of three SNPs of *COL1A2* gene, namely rs42524in exon28, rs1800238 in exon32, andrs2621215in intron46, with CA, a positive association between SNP allele GC rs42524in exon28 with disease has shown (p = 0.02). Other polymorphisms showed no significant associations. The study [23] tested 9.4 million genetic variants to identify associations with the risk of saccular CA in the Finnish population. Four new loci associated with risk CA were identified (2q23.3; 5q31.3; 6q24.2; 7p22.1).

In the study [13] three polymorphisms of *EDNRA* gene (rs5335, rs6842241 and rs6841581) were genotyped to investigate the association with sporadic CA, as well as the size of the aneurysm. There was found no significant differences in the frequency distribution of genetic variants of the gene *EDNRA* between patients and the control group, but it was found that the GG rs6841581 genotype correlates with the size of aneurysms. Thus, it was established that the polymorphism rs6841581 of *EDNRA*gene has a significant association with the size of CA, indicating a possible role for the gene *EDNRA*in genetic mechanisms of CA development and rupture [13].

Association of endothelial nitric oxide synthase *eNOS* with the spontaneous CA risk and aneurysms sizewas investigated in the study [6]. It was studied two polymorphic loci (G-894T and T-786C) in *eNOS* gene. GG genotype G-894T polymorphism was associated with a higher risk of CA, compared to the GT and TT genotypes (OR = 1.897, 95% CI: 1.023 – 3.519, p = 0.04). Patients with CA had a higher frequency of allele C of polymorphism T-786C, compared to the control group. C allele was associated with a higher risk of CA, compared to T allele (OR = 2.116; 95% CI: 1.073 – 4.151, p = 0.030). It was found no significant relationship between *eNOS* gene polymorphisms with the size of the aneurysm. Thus, it was concluded that the *eNOS* gene may be involved in the occurrence and development of CA. The study [7] conducted in a population of India; it was shown that a gene *VCAN* is a candidate gene involved in the pathogenesis of CA. The study confirmed the previously detected rs251124 polymorphism association with the CA risk, as well as identify new association polymorphism rs2287926 (G428D) with the disease.

The study [16] found a new area associated with the CA risk, located on chromosome 7, which has been described as being associated with ischemic stroke and artery occlusion of large diameter, suggesting a possible genetic link between this subtype of stroke and intracranial aneurysms [16]. The study [18] conducted in Dutch and Finnish populations studied the relationship of individual alleles of SNP, associated with the CA, the localization of aneurysms in the middle cerebral artery (MCA) and rupture of the aneurysm at a young age. The authors concluded that genetic factors play a more significant role in the development of aneurysms, localized in the middle cerebral artery, compared to aneurysms in the other sites. This phenomenon, indicating the genetic aneurysms heterogeneity depending on location, must be taken into account in future genetic studies [18].

CONCLUSION

Thus, these studies suggest that the development and rupture of cerebral aneurysms are due to a complex interaction of modifiable factors and genetic predisposition. Search for risk factors conducted in different directions, including the epidemiology of stroke, clinical and experimental studies, and genetic studies. The discovery of new risk factors of the disease, including genetic, contributes to the understanding of mechanisms of cerebral aneurysms, and could be the basis for the future direction of individualized prevention of subarachnoid hemorrhage.

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