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Review article

The role of inflammation and potential pharmacological therapy in intracranial aneurysms

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ABSTRACT

Intracranial aneurysms remain important clinical concern. There is relatively low risk of rupture of symptomless aneurysms incidentally found in MRA or CTA performed due to other indications. Not all of the intracranial aneurysms should or can be treated with neurosurgery intervention or endovascular embolization. Clinical strategy for small, symptomless, unruptured aneurysms is still questionable. Mechanisms underlying aneurysms formation, progression and rupture are poorly understood. Inflammation is one of the factors suspected to participate in these processes. Therefore the aim of this manuscript is to present current state of knowledge about the role of inflammation in the formation and progression of intracranial aneurysms and in their rupture process. Current knowledge about possible pharmacological treatment of intracranial aneurysms will also be presented. Macrophages infiltration seems to participate in the formation of intracranial aneurysms. Inhibition of signals sent by macrophages may prevent the aneurysms formation. Inflammation present in the wall of the aneurysm seems to be also related to the aneurysm's rupture risk. However it does not seem to be the only cause of the degeneration, but it can be a possible target of drug therapy. Some preliminary studies in humans indicate the potential role of aspirin as a factor that decrease the level of inflammation and lower the risk of rupture of intracranial aneurysms. However further research including a greater number of subjects and a prospective randomized design are necessary to assess the role of aspirin in preventing strategy for small, symptomless, unruptured intracranial aneurysms.

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1. Introduction

Intracranial aneurysms remain important clinical issue due to its high prevalence in general population. According to American Heart Association Statistics Committee and Stroke Statistics Subcommittee [1] in every 1 000 000 adults of mean age of 50 years about 32 000 have intracranial aneurysm. Every year about 80 of them rupture causing subarachnoid hemorrhage that can be the cause of death of about 50% of patients. About 1/3 of patients who survive will likely suffer from a major neurological deficits. Only neurosurgery intervention or endovascular embolization is medical treatment strategy to prevent rupture or to treat ruptured aneurysms. Both procedures are not fully safe for patients and are associated with the risk of complications, including death. Up to now there is no recognized pharmacological strategy for aneurysms treatment.

The risk of rupture of symptomless aneurysms, which were incidentally found in MRA or CTA performed due to other indications, is relatively low [2]. There is no definite method that can predict this risk, as it is related to gender, age, size of aneurysms, its location and irregular shape, growth time, coexistence of other vascular lesions, family history of SAH and prior SAH. Smoking, excessive alcohol consumption and hypertension are the only modifiable risk factors [2]. In American Heart Association/American Stroke Association 2015'Guidelines [2] there is no indication which aneurysm size should be treated. Also in European Stroke Association 2013'Guidelines lacks such informations [3].

Taking above into account, not all of the intracranial aneurysms should or can be treated by surgery or endovascular embolization. One of the obstacles can be the lack of patients consent or technical problems including atherosclerosis in blood vessels, location of aneurysms, making surgical or endovascular access difficult or even impossible. This cause a question about the clinical strategy for small aneurysms, not included to the treatment. In these cases only regular MRA or CTA examinations are recommended [2]. However there is a lack of optimal time interval for such check-ups [2]. Another problem is the anxiety associated with potential rupture. Patients knowing about intracranial aneurysm in their heads ask for the treatment. Argumentation that the risk of rupture is low or lower that the risk associated with neurosurgery intervention or endovascular embolization can be difficult to accept by some patients. Recent study by Yamashiro et al. [4] showed that preoperative and postoperative quality of life of patients with intracranial aneurysms is significantly limited. Potential pharmacological therapy in above cases seems to be a reasonable solution.

Mechanisms regulating aneurysms formation, progression and rupture are poorly understood. Inflammation is one of the factors suspected to participate in these processes. Detailed analysis of particles taking part in this state seems to lead to identification of therapeutic targets and creation pharmacological strategy which should inhibit the ruptures. Therefore the aim of this manuscript is to present current state of knowledge about the role of inflammation in the formation and progression of intracranial aneurysms and in their rupture process. Also current knowledge about possible pharmacological treatment of intracranial aneurysms will be presented.

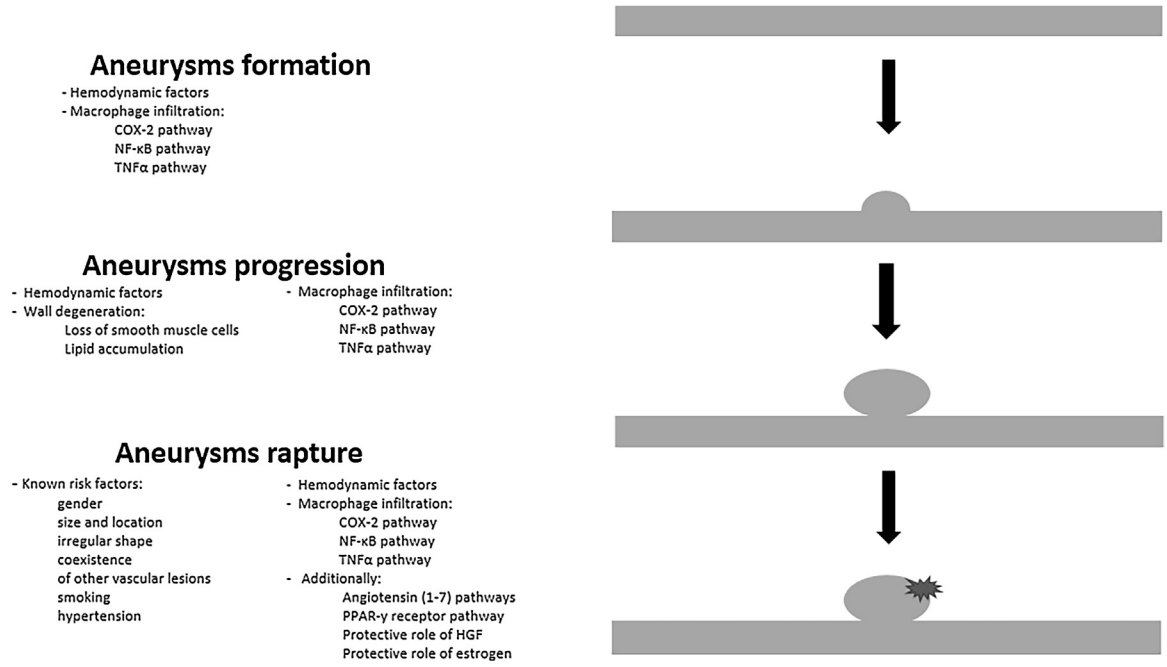
2. Formation of intracranial aneurysms

In most of human intracranial aneurysms it is impossible to say when and how aneurysm occurred. That's way all of the studies investigating aneurysms formations are based on animals. In one of the first studies by Kanematsu et al. [5] mice aneurysms were induced using a combination of single injections of elastase into the cerebrospinal fluid and angiotensin II induced hypertension. Next in the half of mice the reduction in the number of macrophages was induced using clodronate liposome. In the group without blocked macrophage the occurrence of aneurysms was 6 out of 10; in the group with blocked macrophage – 1 out of 10, what suggest that reduction in the number of macrophages inhibits the formation of aneurysms. In the same study [5] also reduced incidence of aneurysms in mice lacking monocyte chemotactic protein-1 (MCP-1), which is critical chemotactic factor for proper macrophage function, compared with the incidence of aneurysms in wild type mice, were observed. Secretion of proteases destroying stromal tissue (matrix), triggering oxidative stress and secretion of inflammatory cytokines can link macrophages with the process of aneurysms formation. What is more, Aoki et al. [6], based on mice and rats with induced aneurysms studies, suggested that induction of macrophage activity is based on cyclooxygenase 2 (COX-2) pathway activation and prostaglandin E (PGE2) via prostaglandin E receptor (EP2) through an amplifying loop and activation of nuclear factor-κB (NF-κB) in the endothelium of the cerebral arteries. It was also suggested in latter study be Aoki et al. [7] that blocking tumor necrosis factor α receptor (TNFαR1) for TNF reduced the formation of aneurysms. These results were confirmed by other authors [8]. In the study by Nuki et al. [9] metalloproteinase-9 (MMP-9) knockout mice, but not MMP-2 knockout mice, had a reduced incidence of intracranial aneurysms. Metalloproteinases, produced mainly by macrophages, are thought to destroy arterial wall extracellular matrix.

The role of the most important inflammation pathways in the formation, progression and rupture of intracranial aneurysms is illustrated in Scheme 1.

Later studies focused on pharmacological agents, which can inhibit above described processes. In the study by Nuki et al. [9] doxycycline, a broad-spectrum MMP inhibitor, reduced the incidence of aneurysm to 10%. Among others, treatment with simvastatin, pitavastatin, pravastatin, nifedipine, olmesartan, ibudilast and erythropoietin (EPO) [10–15] suppressed the development of intracranial aneurysms in different mechanisms. All above studies were also based on animals, however the drugs used in them should be a candidate for medical treatment strategy of intracranial aneurysms in humans. Moreover, COX-2 inhibitors like aspirin or indomethacin [16] should be taken into account.

Summarizing, the inflammation seems to participate in the formation of intracranial aneurysms. Pharmacological inhibition of macrophage infiltration and signaling (via the COX-2 or NF-κB or TNFα pathways inhibition) may inhibit the formation of aneurysms.



Scheme 1 – The role of the most important inflammation pathways in the formation, progression and rupture of intracranial aneurysms.

3. Progression of intracranial aneurysms

The role of inflammation in the progression process of intracranial aneurysms were also studied before. However, most of the above cited authors did not distinguish clearly between aneurysm formation and progression. What is more, below-described studies on rupture of intracranial aneurysms involved data about intracranial aneurysms wall destruction, so that progression process. Studies on progression or growth of aneurysms in general seems to need longer follow-ups so that seems to be more difficult to design.

Starke et al. has shown that inhibition of TNFα by 3,6′dithiothalidomide (DTH) reduce progression of intracranial aneurysms in rats [8]. It was also shown in rats that simvastatin suppresses intracranial aneurysms progression. Statins seem to inhibit the expression of several matrix metalloproteinases, including MMP-2 and MMP-9 involved in inflammation [10]. Furthermore, the similar suppressing effect was observed in the study with pitavastatin. In this case reduction in progression of intracranial aneurysms were explained by inhibition of NF-κB by pitavastatin [11]. Also nifedipine through inhibition of NF-κB suppressed intracranial aneurysms progression in the study by Aoki et al. [12]. Further studies tried to focus on destruction and remodeling of aneurysm wall. Marbacher et al. [17] induced in rats 24 saccular aneurysms of the abdominal aorta – in half of them number of mural cells were reduced. Aneurysms with the reduced number of mural cells were growing and 50% of growing aneurysms ruptured in comparison to not growing. As concluded, the loss of mural cells causes an increase in the size of aneurysm and its rupture. This observations were confirmed by further study in which a transplantation of smooth muscle cells into the luminal thrombus of intracranial aneurysms in rats reduced their destruction resulting in lower recurrence and lower growth of aneurysms [18]. On the other hand, there is no direct evidence that the complement activation affects directly smooth muscles cells [19] and there is no direct evidence on apoptosis induction by inflammatory cells (activation of Caspase 8) in the wall of aneurysms in humans. This indicates a potential role of other factors in the activation of apoptosis process. In this field, the role of Caspase 9 and oxidative stress response is suspected [20]. Also hemooxygenaze-1, secreted by certain inflammatory cells, accompanies the destruction of the walls of aneurysms and ruptures [20]. Recently Ollikainen et al. [21,22] have indicated the presence of mast cells and lipid accumulation in the aneurysms wall and its contribution to remodeling and destruction of this wall.

Another problem related to the progression of intracranial aneurysms is their morphology which seems to be linked to hemodynamic factors and inflammation. Irregular shape, particularly presence of daughter sac, seems to be related to higher risk of rupture. In the recent study by Abboud et al. [23] risk of rupture increased from single sac with regular margin, through aneurysms with irregular margin and with daughter sac, and was the highest in multilobulated intracranial aneurysm. Formation of daughter sac in intracranial aneurysms seems to be related to hemodynamic factors causing local elevation of pressure at the site of aneurysms without surrounding structure, which may cancel perpendicular wall tension [24]. However, it seems that there are no studies investigating the role of inflammation factors on the formation of daughter sac in intracranial aneurysms.

In spite of the small amount of studies focusing only on progression of intracranial aneurysms all cited studies indi-

cate that the inflammation may participate also in this process. Pharmacological inhibition of macrophage infiltration and signaling (via the COX-2 or NF-κB or TNFα pathways inhibition) may inhibit also the progression of intracranial aneurysms.

4. Rupture of intracranial aneurysms

It is difficult to predict which aneurysm will rupture and cause hemorrhages. It is suggested that the risk of rupture of intracranial aneurysms is related among other to gender, size of the aneurysm, its location and irregular shape, coexistence of other vascular lesions, smoking and hypertension [2,25–28]. However this does not exclude that other factors especially on biochemical level take part in this process. Frösen et al. [29] in histological examination of the material obtained during neurosurgical clipping of human 24 unruptured and 42 ruptured intracranial aneurysms found an increased infiltration of macrophages and proliferation of smooth muscle cells in ruptured aneurysms. In addition, in ruptured aneurysms M1/M2 subsets of macrophages balance was lost in favor of M1 proinflammatory cells [30]. Level of metalloproteinases, produced by macrophages, seems to be higher in ruptured than in unruptured aneurysms in humans [31]. In histological examination of the material obtained during neurosurgical clipping of human intracranial aneurysms Tulamo et al. [19] found that in addition to the macrophages infiltration, an activation of complement (humoral response) in ruptured aneurysms is present. In the histological examination by Gounis et al. [32] of the material obtained during the clipping of 20 unruptured and 3 ruptured human intracranial aneurysms, all ruptured aneurysms had increased myeloperoxidase activity. In another study a 2.7-fold higher concentration of myeloperoxidase was found in blood drawn directly from the lumen of intracranial aneurysms in comparison to peripheral blood [33]. It can be concluded that myeloperoxidase, secreted mainly by neutrophils and macrophages, results in oxidative stress and is accompanied by an increased risk of aneurysms rupture.

As discussed, many studies confirmed that inflammation accompanies the rupture of aneurysms in humans. There are other factors like loss of smooth muscle cells that seems to contribute to destruction of aneurysms wall and to the ruptures of aneurysms, as well. Some inflammatory cells may cause oxidative stress and this in turn may affect the ruptures of aneurysms.

It is unknown how well-known risk factors like smoking or hypertension [2,25–28] can affect or trigger the inflammation and cause rupture. Recent study on humans by Cebral et al. [34] indicated that flow conditions in saccular intracranial aneurysms, assessed on the basis of patient-specific computational models of hemodynamic (computational fluid dynamics – CFD) created from preoperative CT angiographies were associated with wall remodeling. More diffuse inflow was associated with degenerated and decellularized saccular aneurysm walls, assessed in histological examinations of material obtained in neurosurgical clipping. Also low flow conditions were associated with wall changes. These observations suggest that endothelial injury may be a mechanism by which flow induces the inflammation in the intracranial aneurysms wall. Also Jamous et al. [35,36] indicated that endothelial cell injury is the earliest change in aneurysm wall. However there are many controversy about the role of hemodynamic factors on the rupture risk of intracranial aneurysms [34,37–39]. In the last review and meta analysis study Can et al. [37] showed that increase in wall shear stress (WSS), defined as tangiental frictional force exerted by flowing blood on the arterial endothelium, proportional to the blood viscosity and velocity gradients [38], may contribute to aneurysms formation, whereas low WSS seems to be associated with raptured aneurysms. It can be explained that high WSS implicates wall remodeling and potential destruction via endothelial injury. Low WSS, on the other hands, can cause localized stasis of blood flow near the aneurysms wall causing endothelial dysfunction and elevation of proinflammatory factors [37,39]. Interpretation of the results of studies on hemodynamic factors remains difficult, while among others except WSS other indexes have been proposed and used [37], there are differences induced by diverse configurations and geometries of vessels of the anterior and posterior circulations [40]. Furthermore, some studies investigating hemodynamics factors were performed for sidewall aneurysms, while others – for bifurcation aneurysms [37].

There is a group of other factors involved in rupture process. It cannot be excluded that they modify above described observations. As proved by Pena Silva et al. [41] angiotensin (1–7) via Mas receptor reduces the formation of intracranial aneurysms and reduces their rupture probability. Shimada et al. [42] indicated also the protective role of angiotensin (1–7) however via angiotensin II type 2 receptor (ATR2) pathway. What is more, angiotensin (1–7) in this study reduced the expression of TNFα. In another study Shimada et al. [43] showed that activation of PPAR-y (Peroxisome Proliferator-Activated Receptor-y) on macrophages by pioglitazone (PGZ) reduced macrophages infiltration and level of inflammatory cytokines (interleukin-1 and interleukin-6) resulting in decreasing aneurysm rupture risk. Hasan et al. [44] confirmed this results, indicating the important role of smooth muscle cell PPAR-y. Pena Silva et al. [45] suggests that hepatocyte growth factor (HGF) reduces inflammation and prevents rupture of intracranial aneurysms. In another study by Tada et al. [46,47] estrogen (via β receptor for estrogen) seems to prevent the rupture of intracranial aneurysms. This seems to stay in line with clinical observations that the prevalence of hemorrhage caused by intracranial aneurysms rupture in postmenopausal women is higher than in premenopausal women [48]. Also hormonal replacement therapy (HRT) including estrogens seems to decrease rupture risk in postmenopausal women [49]. All above studies were based on animals.

Furthermore, comparison of gene expression by Kurki et al. [50] of 8 ruptured and 11 unruptured human aneurysms showed that the accumulation of lipids was strongly linked with rupture. Additionally, this seems to be linked to the fact that lipid accumulation in the wall of aneurysms is associated with loss of wall cells [51] and is associated with an activation of the complement system [52]. On the other hand, Pyysalo et al. [53,54] showed the presence of the bacterial DNA specific to the mouth in the intracranial aneurysms. This results raised

the question about potential role of bacteria in the formation and rupture of intracranial aneurysms.

Summarizing, inflammation in the wall of the aneurysm seems to be accompanied by destruction of the wall and the risk of rupture. This suggest a potential role of inflammation as a marker of rupture risk. If proper assessment tool is created, we will be able to recognize aneurysms with high risk of rupture and treat only them. This can be also useful in case of SAH and multiple intracranial aneurysms, when it is impossible to say which aneurysm caused hemorrhage. Assessing the inflammation state should help clinicians to indicate this aneurysm [55,56]. Secondly, inflammation does not seem to be the only cause of the destruction of the wall of the aneurysm, but it can be a possible target of drug therapy.

5. Perspectives of possible pharmacological treatment of intracranial aneurysms

There are some studies focusing on the role of aspirin as a well-known agent against inflammation. Except for blocking COX-2 and microsomal prostaglandin E2 synthase 1 (mPGES-1), aspirin was shown to inhibit MMP-2 and MMP-9 expression [57], TNFα in smooth muscle cells [58] and to reduce NF-κB activity [58,59].

In the study by Li et al. [60], firstly intracranial aneurysms in rats were induced. The group was divided into aspirin-treated and untreated control group. Then the aneurysms wall were histologically examined. As concluded, aspirin reduced the destruction of the wall of the aneurysm and lowered inflammatory markers (reduced expression of MMP-2 and MMP-9, reverse upregulation of NF-κB, MCP-1 and vascular cell adhesion molecule-1 – VCAM-1).

A retrospective evaluation by Hasan et al. [61] of 271 untreated aneurysms of patients from International Study of Unruptured Intracranial Aneurysms (ISUIA), in which patients were divided on the basis of interview into group using aspirin (≥3 times a week) and groups of nonusers of aspirin (''less than once o month'' and ''between once a month and twice a week''). In the group of patients taking aspirin (≥3 times a week) a fewer incidents of aneurysms ruptures were observed. Another retrospective assessment of 1797 patients with intracerebral haemorrhages and 1340 patients with SAH by Garcia-Rodriguez et al. [62] showed that aspirin was not associated with the risk of intracerebral bleeding, however chronic low-dose of aspirin (75–300 mg/day) reduced the risk of SAH. Results of the retrospective study by Gross et al. [63] of 747 patients with brain aneurysms indicated that the risk of SAH is lower in the group receiving aspirin compared to those not taking it (28% vs 40%). However in this study among patients with SAH there were no significant difference in presenting clinical and radiological grade, measured by Hunt-Hess and Fisher Scales, between patients taking and not-taking aspirin. What is more, aspirin use was not associated with 1-year poor outcome.

Another study design was proposed by Hasan et al. [64]. In this study 11 patients with intracranial aneurysms were divided into two groups: 6 people – treated with aspirin (81 mg/day) and 5 people – control group. Initially inflammation in aneurysms wall was assessed in MR enhanced with Ferumoxytol. After three months second MR scanning was performed to assess the inflammation process. Then, surgical clipping of aneurysms was performed and obtained material was histologically examined. Both histological and MR results suggested that aspirin reduced inflammation in the wall of aneurysms. Ferumoxytol used in this study is a relatively new nanoparticle containing iron oxide coated by carbohydrate shell. It belongs to ultrasmall superparamagnetic iron oxide (USPIOs) and was initially developed for threating iron deficiency anemia in patients with chronic renal failure [65]. It can be used as enhancement medium and T2*-weight gradient-echo imaging is usually applied for evaluation of macrophage infiltration within the aneurysms wall. Ferumoxytol is usually administered intravascular about 24–72 h before MR imaging. In this time it is absorbed by macrophages and they, as mentioned above, accumulate in the area of inflammation [66–68].

Objective comparison of above described studies is difficult because of their limitations like relatively small sample size. Presence of potential confounding variables should be also taken into account. It should be emphasized, that most of studies on humans had retrospective design and doses of aspirin used in particular studies were different. However, on the basis of all above preliminary studies in animals and humans, it seems that small doses of aspirin can reduce the risk of aneurysms rupture. Further research including a greater number of subjects and prospective randomized design to assess the role of aspirin as a potential preventing strategy for small, symptomless, unruptured intracranial are inevitable.

It is worth to mention that some of authors indicate the possible role of another pharmacological agents like tetracycline (minocycline and doxycycline) in prevention of intracranial aneurysms rupture [69]. However this study, like most of the above, was based on mice. Also previously mentioned statins and other medications [10–15], blocking formations of intracranial aneurysm in animal's models, should be taken into account as potential prevention strategy. However initial studies with statins performed on humans gave inconclusive results [70–72].

6. Conclusion

Following above review of literature (however not a systematic review) it can be concluded that inflammation appears to mediate in the formation and progression of intracranial aneurysms and seems to be related to its rupture risk. This suggests a potential role of inflammation as a marker of aneurysm's rupture risk. Furthermore, inflammation can be a possible target for drug therapy. Preliminary studies on animals and humans indicate that small doses of aspirin can reduce the risk of aneurysms rupture. However further research including greater number of subjects and prospective randomized design are necessary to assess the role of aspirin as a potential preventing strategy for small, symptomless, unruptured intracranial aneurysms.

Conflict of interest

None declared.

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