Огляди

УДК 616.831

HEMORRHAGIC STROKE AS POST-INTRACEREBRAL HEMORRHAGE INFLAMMATION

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Intracerebral hemorrhage remains one of the less studied problems in modern neurology. Later publications suggest that inflammatory processes play a significant role in hemorrhagic stroke; however, most of these reports represent fragmentary information on the local and less system levels of inflammation, and do not show the correlation between these levels. In this review the attention is focused on the compensatory, adaptive and restorative nature of the inflammation in the post-intracerebral hemorrhage damage. Non-complicated and complicated forms of inflammation are discussed regarding their influence on the course and outcomes of hemorrhagic stroke. Optimization of complicated inflammation could be one of the approaches for improving the outcomes of hemorrhagic stroke.

KEY WORDS: hemorrhagic stroke, intracerebral hemorrhage, inflammation, pathogenesis, outcome, treatment

ГЕМОРАГІЧНИЙ ІНСУЛЬТ ЯК ЗАПАЛЕННЯ ПІСЛЯ ВНУТРІШНЬОМОЗКОВОГО КРОВОВИЛИВУ

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Внутрішньомозковий крововилив залишається однією з найменш вивчених проблем сучасної неврології. Останні публікації показують, що запальний процес відіграє важливу роль в геморагічному інсульті, проте більшість з них представляють уривчасті відомості про місцеві і, менше, системні рівні запалення, а також не показують зв'язків між цими рівнями. У цьому огляді увага зосереджена на компенсаторному, адаптивному і відновлювальному характері запалення в загоєнні місця пошкодження після внутрімозкового крововиливу, обговорюються неускладнені та ускладнені форми запалення та їх роль в перебігу і витоках геморагічного інсульту. Оптимізація ускладнень запалення може бути одним з підходів для поліпшення результатів геморагічного інсульту.

КЛЮЧОВІ СЛОВА: геморагічний інсульт, внутрішньомозковий крововилив, запалення, патогенез, наслідки, лікування

ГЕМОРРАГИЧЕСКИЙ ИНСУЛЬТ КАК ВОСПАЛЕНИЕ ПОСЛЕ ВНУТРИМОЗГОВОГО КРОВОИЗЛИЯНИЯ

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Внутримозговое кровоизлияние остается одной из наименее изученных проблем современной неврологии. Последние публикации показывают, что воспалительный процесс играет важную роль в геморрагическом инсульте, однако большинство из них представляют отрывочные сведения о местных и, меньше, системных уровнях воспаления, а также не показывают связей между этими уровнями. В настоящем обзоре внимание сосредоточено на компенсаторном, адаптивном и восстановительном характере воспаления в заживлении места повреждения после внутримозгового кровоизлияния, обсуждаются неосложненные и осложненные формы воспаления и их роль в течении и исходах геморрагического инсульта. Оптимизация осложнений воспаления может быть одним из подходов для улучшения результатов геморрагического инсульта.

КЛЮЧЕВЫЕ СЛОВА: геморрагический инсульт, внутримозговое кровоизлияние, воспаление, патогенез, исходы, лечение

Introduction

Stroke is the second main cause of death worldwide and a major cause of mortality and morbidity [1–3]. Among the different types of stroke, hemorrhagic stroke remains the one that is less studied as it develops after the rupture of the blood vessel in the brain [4–6].

Hemorrhagic stroke is accounted in 20 % of stroke cases [7, 8]. Thirty percents of the patients die within the first month after the occurrence of hemorrhagic stroke, 23 percents of patients die after a year and 65 % of survivors can function independently [9–11]. The rest of the patients remain significantly disabled and may need considerable help with daily tasks [12–15].

Stroke costs the National Health System (NHS) and the economy about £7 billion a year: £2.8 billion in direct costs to the NHS, £2.4 billion of informal care costs (e.g. the costs of home nursing borne by patients' families) and £1.8 billion in income lost to productivity and disability [16] . The total costs of stroke care are predicted to rise in real terms by 30 per cent between 1991 and 2010 (Reducing Brain Damage: Faster access to better stroke care. National Audit Office 2005, http://www.stroke.org.uk).

In the pathogenesis of hemorrhagic stroke the most significant attention is given to hematoma expansion [17], cell death processes (apoptosis and necrosis) [18–20], the effects of blood degrading components on surrounding tissues (erythrocytes, hemoglobin, iron) [21–23], thrombin-toxicity effects [24–28], proteases activity (mainly represented by studies done on matrix metalloproteinases activity) [29–32] and perihematoma oedema formation [33–36], Only in recent years studies started to pay interest to the contribution of inflammatory processes into the progression of stroke [37–40, 1, 41]. Although reports are limited the implications of some inflammatory markers from activated neutrophils and microglia have been evaluated. These include primarily cytokines such as TNF-a, ICAM-1, IL-6 and NF-kB as well as vasoactive mediators such as superoxide anion, thromboxane A_2, endothelin-1, prostaglandin I_2 and prostaglandin H_2 [42–48]. However, most of the studies so far have focused mainly on the local processes not taking into account the contribution of system reactions, which are responsible for organization and supply of any inflammatory response [41, 49, 38, 50]. From a basic perspective, it is understandable to consider hemorrhagic stroke as a recovery process involving inflammatory reactions in response to intracerebral bleeding, which is realized at the local and system levels, what we suggest in our review.

Intracerebral hemorrhage

An intracerebral hemorrhage is bleeding in the brain caused by the rupture of a blood vessel and commonly occurs in the cerebral lobes, basal ganglia, thalamus, brain stem (pons) and cerebellum [51–53].

In most of the cases intracerebral hemorrhage results from rupture of small penetrating arteries, which originate from basilar arteries or middle, anterior, or posterior cerebral arteries. Microscopial studies suggest that most of ruptures occur at or near the bifurcation of affected arteries [54].

Formation of hematoma was shown to be not a monophase process, as in some cases the bleeding continues up to 24 hours [55, 56]. Beside the damage from hematoma to the brain tissues, its extending also results in midline shift, pressing healthy brain tissues against the skull and thus promoting ischemic processes that ultimately contribute to neurological deterioration [33] and brain atrophy [57].

The distribution of the blood into the tissue surrounding the brain has a space-occupying effect, moving tissues apart and filling space in between them or distributing in between cells, thus disturbing the natural conductive pathways resulting in clinical outcomes [57, 58].

Characteristics of the blood leakage are determined by many risk factors, concomitant diseases, location and distribution of the hematoma and general state of the body (stressed, distressed) [4, 3].

Post-hemorrhage clots undergo enzyme destruction and evacuation with further connective-tissue replacement through inflammation [59–62]. During clot destruction a variety of products are released [63] modulating inflammation and thus having an impact on the type of outcomes.

Inflammation

Intracerebral hemorrhage, being a pure injury by its nature, triggers inflammatory responses [64, 40, 65, 66, 1].

Inflammation is a protective process evolving as a reaction of the organism to injury and represents an integrated adaptive mechanism aimed at maximizing the recovery and restore the integrity and functionality of damaged tissues. Inflammation is characterized by a biphasic response involving stress and adaptation and it is controlled at local and systemic levels with the aim to eliminate and replace necrotizing and destroyed tissues with connective ones [67, 39, 68, 69].

Pain, redness, swelling, heat and loss of function are classical markers representing local

symptoms of inflammation. In contrast, systemic symptoms of inflammation are represented mainly by fever, leukocytosis, immunological, humoral and neural reactions that are known as «adaptation syndrome».

Local level of inflammation

Local inflammation is developed as a reaction to rapid formation of hematomas and realized through buffer perihematoma zone, which undergoes certain changes due to its demands.

Most of studies aimed at understaning perihematoma it was suggested to be the same as ischemic penumbra in the conditions of ischemic stroke [70, 57, 71]. However, numerous later studies proved it wrong, showing an absence of ischemic processes in perihematoma zone and indicating hypoperfusion only [72–74].

The size of perihematoma and hematoma zones have also been one of the reason of discussions and remain controversial till today [70], as sometimes perihematoma could be found even bigger than hematoma itself. From perspective of inflammatory response in hemorrhagic stroke zone, it is important for perihematoma zone to be of the proper size for providing inflammatory response running. As it was shown on the example of myocardial infarction the size of peri-infarction zone play an important role in outcomes [75–77]. Communicative properties of perihematoma zone are mainly represented by vascular changes in the region.

Vascular changes

Local level of inflammation include vascular changes such as vasodilatation, increased permeability of vessels,widened intracellular junctions and contraction of endothelial cells due to the release of several substances such as histamine, VEGF, bradykinin, nitric oxide and other bioactive molecules [78–79, 57, 80–81]. Most of the vascular changes in response to inflammation take place in the perihematoma zone and are aimed at facilitating the entrance of responsible competent cells. For example, adhesion between leukocytes and endothelial cells can be elicited by a number of agents such as superoxide, lactoferrin, histamine, Il-1, hydrogen peroxide, and others produced in the perihematoma zone [82, 23, 45, 83–85].

Nitric oxide (NO), a biologically active gas synthesized by a variety of cells including the vascular endothelium, is an important mediator of vascular events such as vasodilatation [86–88], inhibition of platelet aggregation and modulation of platelet-leukocyte adhesion [89].

Carbon monoxide (CO), another gas produced endogenously from heme degradation by heme oxygenase pathways also possesses important vasodilatory properties [90–92], thus contributing to cell adhesion and migration from main blood stream into the region of injury [93]. Notably, an increase in CO concentrations in the brain tissue surrounding hematoma is commonly observed in patients [94].

Oedema

Oedema develops straight after intracerebral hemmorhage [45, 95–96, 20, 97]. In animal experimental models of hemorrhagic stroke, oedema was shown to peak around day 3–4 and to decrease slowly after. In humans, oedema peaks on day 3 and decreases by day 10–20 after the occurrence of hemorrhagic stroke. Whether perihaematomal oedema contributes to the hemorrhagic stroke damage still remains unclear. As it was shown in various reports [33–34] oedema formation is associated with poor outcome in patients. However, Gebel et al. showed that the presence of oedema in the first few hours after hemorrhagic stroke results in good outcome [35].

The formation of oedema occurs in several phases. The first few hours after intracerebral hemorrhage are characteirzed by hydrostatic pressure and clot reactions with movement of serum from the clot into the surrounding tissues 36. Thrombin production and the coagulation cascade are the next processes being activated. Besides having vasogenic nature, oedema also develops as a result of toxicity of certain blood degrading components and cell metabolites, such as heme and TNF-α, [45, 17, 98–100].

Indicated hypoperfusion in perihematoma zone may contribute to leukocyte rolling, adhesion and extravasation and it has been suggested that slow flow rate may contribute to neutrophil recruitment [80] and further necrotized tissues evacuation and replacing it with neuroglial scar. Later studies suggested that oedema is represented mainly by the predominant cellular component [101], which is necessary factor in inflammatory recovery of the post-hemorrhagic brain damage. The quality of the scar is also determined by lots of the factors, including microcirculation and oedema.

The importance of brain oedema in the conditions of intracerebral hemorrhage was also indirectly shown by Bereczki et al. in their study using mannitol, an osmotic agent and a free radical scavenger, which did not have any major effect [102].

Chemotaxis, cell kinetics and dynamics

Blood vessel wall rupture, blood leakage and hematoma formation lead to the process called

alteration, the first stage of the hemorrhagic stroke and very beginning of generation of stress signals which are represented by sympathetic activation and increased functional activity of a hypothalamo-pituitary and adrenal system with the change of functions of all target organs [103–106]. Entry of affected metabolic products from the hemorrhagic stroke zone to the system circulation, further hormones activation, ejection of leukocytes from the bone marrow depot to the systemic blood flow and their further activation and readiness to follow the chemotaxis [107–109]. Since the bone marrow depot mainly contains neutrophils, leukocytosis appears as the shift in cell count; neutrophils are activated and migrate to the hemorrhagic stroke zone by positive chemotaxis [110].

Neutrophil infiltration can be observed within 6 hours after ictus and increases gradually at 6-12 hours and reaches peak at 12-72 hours [45, 40, 111, 48] with slight decrease at day 7 [42]. MacKenzie and Clayton (1999) in study of early cellular events in the perihemorrhage zone in 33 fatal cases of spontaneous hemorrhagic stroke found leukocyte infiltration to be present as early as 5 to 8 h and disappeared by 72 h [112–113]. Granulocytes were shown to play role not only in destruction of necrotized tissues, but also in stimulation of subsequent recovery processes in the post-hemorrhage conditions [114].

Alteration in hemorrhagic stroke zone triggers further inflammation processes, such as structural and immune blood cells migration, proliferation, which are activated by stress.

Immune system cells together with cells involved in the area (neurons, astrocytes, damaged cells) release a variety of bioactive substance which play role of positive chemotaxis, attracting more specific and area-appropriate cells from depots, with aim to destroy and eliminate damaged area by phagocytosis (lyzosomal enzymes, free radicals, oxidative burst) [40, 115–116], and at the same time playing role of chemoreppelents, thus regulating inflammatory response to correspond destructive, eliminative and healing processes.

Activated microglia/macrophages are present in perihematoma zone 1–4 hours after hemorrhagic stroke incidence [117–118, 42], reaching the peak on day 7 [119–121].

Reactive gliosis as a part of healing process can be already observed at 24-72 hours post-ictus [39, 68], reaching peak at day 14-21 with following decrease, leaving numerous resting astrocytes [67]. It was shown that mesynchemal stem cells, that are present in a bone marrow, can differentiate not only into mesodermal, endodermal, ectodermal cells, but also into neuronal and glial lineage [122]. Activated neural stem cells were observed already on day 2 around hematoma, increasing at day 4–7, reaching the peak at day 14 with slow decrease after [123–124]. Observing the stem cells activation around hematoma and their migration into the hematoma region also suggest the importance of perihematoma zone, as stem cells might be activated by the local humoral factors [125].

The fact that neural stem cells can migrate into the post-hemorrhagic zone only at the defined time after the disposal of damaged tissues was indirectly being proven in the study by [126–128] when it haven't been achieved the results being trying to saturate hematoma zone with neural stem cells 2 and 24 hours post-ictus.

These processes play an important role in both freeing the zone from necrotized tissues and forming on its place the primary connective tissue with further organization into one of the variety of neuroglia.

Importance of local humoral factors

NMDA and Calcium

On the molecular level perihematoma zone around hematoma is greatly influenced by overreaction of glutamate and aspartate, which in normal state are stored in synaptic terminals, are rapidly ejected from extracellular space [129–131]. This process is called excitotoxicity and leads to opening of the calcium channels associated with N-methy1-D-asapartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxanole propionate (AMPA) receptors [132]. Intracellular calcium is responsible for activation of several destructive enzymes such as proteases, lipases, and endonucleases that allow release of cytokines and other mediators of inflammation [133–135].

Cytokines

Cytokines are bioactive molecules secreted in stress region by activated cells, which play a role in regulation of immune response on all the levels of its progression [40, 136]. Cytokines provide a variety processes such as proliferation and differentiation of cells, chemotaxis, antigen expression of different markers, activation of immunoglobulin secretion, macrophages cytotoxicity induction, etc. [132, 136]. These molecules are usually classified as pro- and anti-inflammatory cytokines.

It was shown that cytokines are produced by many cells in the brain, such as microglia, astrocytes, neurons, endothelial cells [137–138, 44, 139]. However, the principal source for cytokines in the brains is activated microglia/

macrophages [65]. However, there is also an evidence of involvement of peripherally derived cytokines [140]. After hemorrhagic stroke ictus the permeability of blood-brain-barrier increases [141] thus leading to migration of mononuclear phagocytes, T-lymphocytes, natural killer cells, and polymorphonuclear neutrophilic leukocytes, which produce and secrete cytokines [142].

It was shown that pro- and anti-inflammatory cytokines can induce and potentiate other cytokines and activate positive and negative feedback [1]. It should be considered that many of cytokines, e.g. TNF-α, play double role in inflammation, acting as pro- and as anti-inflammatory cytokine.

In studying of hemorrhagic stroke pathogenetic mechanisms the most important role was given to TNF- α, IL-1b, IL-6 and IL-8 [40]. It was shown an elevation of IL-1b and TNF-α level at 3-24 hours post ictus in a double-injection autologous blood injection rat model of hemorrhagic stroke [143]. It the collagenase hemorrhagic stroke model it was observed an increase in TNF- α levels at 4-8 hours post ictus [144]. Studies done by Maine et al. reported that intrastriatal infustion of TNFa-specific antisense oligodeoxynucleotide or adenosine A_{2A} receptor agonists in rats reduced TNF-α mRNA and protein production in brain tissue surrounding a collagenase-induced hematoma [144–145]. The results showed the reduction in perihematoma cell death and improvement in neurobehavioral scoring. However the dual role of TNF-α should be taken into account, as TNF-α can potentially repair or damage injured brain tissue [146].

To date only few studies have been done in patients evaluating cytokines level after hemorrhagic stroke. In a study of 29 patients IL-6 levels have been reported to be increased significantly at day 1 with gradual decrease afterwards [147]. Another study of 124 patients with hemorrhagic stroke showed that elevated plasma concentration levels of TNF-α and IL-6 [148] correlated with the magnitude of the subsequent perihematoma brain oedema.

Studies dedicated to correlation of cytokines levels to local inflammatory response in the conditions of hemorrhagic stroke have not been done yet [149].

Metalloproteases

Metalloproteases have complex properties in the brain in normal and pathological conditions. Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteolytic enzymes involved in the reorganization of the extracellular matrix [32].

A lot of published data show that extracellular proteases are involved in cell death in many neurological diseases [150–151]. The activity of MMPs can be controlled by lots of the factors among which are free radicals, either acting through latent forms or by mRNA induction trhough factor-kappaB factor site pathway [152–153]. MMPs increase permeability of capillaries, contributing to brain oedema [1, 154] and, most probably, facilitating entrance of time-competent cells into the region.

It was also shown that MMPs are essential for neurogenesis, myelin formation, and axonal growth [155–156], thus the ideas of MMPs inhibiting remain controversial. Last studies suggest that inhibition of MMPs facilitates cell death in vivo [157].

Heme-oxygenase and heme metabolism

Heme-oxygenase (HO) a rate-limiting enzyme in heme degradation has two active isoforms, among which are inducible HO-1, also known as heat shock protein, HSP32 (Dwyer et al., 1992; Ewing and Maines, 1991; Maines, 1997), and constitutively active HO-2. In normal conditions HO-1 is barely can be determined in the brain (Chang et al., 2003).

Heme catabolism by HO results in release of ferrous iron, carbon monoxide and billiverdin, which is converted into billirubin by billiverdin-reductase. Billirubin as a result of HO-1 activity was found to be present in neurons and astrocytes and may prevent them from the toxicity [158–160]. Nanomolar concentrations of bilirubin protect neuronal cells from ROS activity [91]. Bilirubin, released from heme metabolism, was also suggested to play certain role in vasodilation in the region hematoma after subarachnoid hemorrhage [161].

The release of ferrous iron, which remains toxic to brain tissues in high concentrations, usually goes in parallel with an increase in ferritin level, the main iron-storage protein in the brain [21].

In the study of hemorrhagic stroke modulation with lysed blood injection, the induction of HO-1 protein was observed in glia surrounding hematoma and immunoreactivity for HO-1 persisted over 4 days [163]. Later, in vivo experiments suggested that HO-1 activation in brain in the conditions of hemorrhagic stroke exacerbates brain injury [164] in early stages. However in later stages, WT animals showed better improvement comparing to HO-1 knock-out animals, suggesting that HO-1 activation might contribute to recovery in later stages of hemorrhagic stroke . HO-1 was shown to reach its peak on day 3 and last for a long period and to be mostly of microglia type [21].

Activity of HO-1 protein also correlates with activation and migration of polymorphonuclear leukocytes, which is observed at 3-7 days, at the time when the recovery processes begin [165–166].

CO, carbon monoxide, small molecular gas that is released from heme catabolism by HO activity, functions as a soluble messenger [167, 91]. Study done by [91, 167] presented inhibitory properties of exogenous CO administration on TNF-a in wild type RAW 264 cells after lipopolysaccharide treatment, suggesting that CO may contribute to modulation of inflamemation. [168–170] have suggested that CO activates anti-inflammatory response by inhibiting the synthesis of the pro-inflammatory cytokines under stress conditions. A CO-releasing molecule (CORM), dimanganese decacarbonyl, was also found to dilate isolated, pressurized cerebral arterioles derived from newborn pigs [89].

Reactive oxygen species

In the conditions of brain injury, reactive oxygen species (ROS) are released by variety of cells, such as neutrophils, endothelium, activated microglia/macrophages [171, 1].

Being an important part of oxidative metabolism, the high concentrations of ROS can lead to lethal circumstances [83]. Reactive oxygen species were shown to contribute to ischemic brain injury (Crack and Taylor, 2005; Saito et al, 2005) and might also contribute to the outcome of hemorrhagic stroke [172–173].

As a result of hemorrhage, the extracellular spaces of the brain become exposed to hemoglobin and its breakdown products. Iron and iron-related compounds, including hemoglobin, catalyze hydroxyl radical production and lipid peroxidation (Sadrzadeh et al, 1987; Sadrzadeh and Eaton, 1988), which expose the brain cells to increased levels of oxidative stress. Indeed, high levels of oxidative stress, as measured by protein carbonyl formation, have been found shortly (within minutes) after the onset of autologous blood injection in pig (Hall et al, 2000; Wagner et al, 2002). In addition, intracerebral infusion of lysed erythrocytes into the rat striatum induced marked brain oedema and profound neurologic deficits (Wu et al, 2002b).

In this setting, increased oxidative stress, measured by protein carbonyl formation, might be associated with reduced Mn-superoxide dismutase and CuZn-superoxide dismutase contents and increased DNA damage.

ROS may also serve as activators for neutrophil chemotaxis [174] suggesting another role for ROS in modulating of inflammatory response. There are also evidences that ROS may serve in physiological vasodilator mechanism in cerebral microcirculation [84]. Later studies report failures in using antioxidant therapy, pointing out deleterious role of ROS in homeostasis, however suggesting that overproduction of ROS may affect the recovery processes [82]. An importance of ROS production for intracerebral hemorrhage was reported by Liu et al. when it was shown the development of adaptive compensatory mechanisms for free radical production in knockout mice [175].

Thrombin

Thrombin is a well known serine protease, one of the main components in the blood coagulation cascade process, is rapidly produced straight after occurrence of the hemorrhagic stroke (Xi, et al., 2006; Xi, et al., 2003).

It was shown that in high concentrations thrombin causes inflammatory reaction, contributing to the brain oedema development and neuronal death [176–178]. Thrombin affects an opening of the blood brain barrier [179–180]. Thrombin-induced brain injury was suggested to be mediated by complement cascade. Injected thrombin caused 7-fold increase in C9 complement complex and its deposition on neuronal membranes [181].

Thrombin also was shown to be one of the stimuli that affect phosphorylation state of the glutamate receptors [182], what lead to opening of the calcium channels of migrated cells and activation of destructive enzymes and further release of cytokines and other mediators of inflammation. Thus thrombin contributed to stage of inflammatory response aimed for cleavage of the damaged region.

Between other beneficial sides of the thrombin activity are such as: thrombin stops bleeding and modulate hematoma enlargement in certain percentage of the patients over the first day. Some studies suggest that low concentrations of thrombin induce protective neuronal effects [183]. Affecting an opening of the blood brain barrier, thrombin facilitates entrance of the competent cells into the intracerebral hemorrhage zone, thus contributing to it recovery via inflammation. Intracerebral injection of thrombin causes gliosis and scar formation [177–187, 184–185].

Thrombin is one of many emphasized components of coagulation system of the body that take place in intracerebral hemorrhage conditions. In the study performed by [26] it was shown that formation of clot does result in early oedema formation, suggesting an importance of the whole coagulation system, thrombin particularly, in inflammatory process and resolution of the problem. [186] reported no differences

between ischemic and hemorrhagic stroke in coagulation system activity, suggesting that haemostatic changes aree consequences of brain damage rather than primary haemostatic activation only.

System level of inflammation

System level of inflammation is mediated throughout mechanisms of stress or adaptation syndrome. Firstly the definition of general adaptation syndrome (GAS) was proposed by Canadian scientist Dr. Selye in 1936, when it was described as complex of general defensive mechanisms in the body of living creatures as a reaction to the impact from strong and prolonged internal and external stimuli. These reactions are to encourage restoration of the disturbed balance and aim to maintain the homeostasis. Factors that induce GAS are called stressors, and the condition of the body – stress.

The main signs of GAS are enlargement of adrenal cortex and amplification of its secretory activity, reduction in spleen size, lymphatic nodes, changes in the blood formula (leukocytosis, lymphopenia, eosinopenia), metabolic disorders with prevalence of breakup processes. Adaptation to unusual conditions is presented by humoral (that come with blood) stimuli (adrenalin, histamine, serotonine, metabolic products of the tissue breakdown), which lead to the activation of adaptive mechanisms, first of all to the activation of reticular formation and hypothalamus-hypophysis-adrenal glands systems.

It was reported an increase of catecholamine level in patients with hemorrhagic stroke, suggesting the peak level to be observed on day 3-6 with gradual decrease thereafter [187].

Glucocorticosteroids, one of the stress hormones play certain role in microcirculation by their ability of vasodilation inhibition and preventing vascular permeability, thus playing anti-inflammatory role in the recovery process [188].

Derex et al. showed that primary adrenocortical insufficiency led to the development of intracerebral hemorrhage, suggesting the cortisol role in the hemorrhagic stroke recovery process [189].

Another system hormone erythropoietin also participates in hemorrhagic stroke recovery, as it was found that hemorrhage in erythropoietin treated group was shown to be reduced by 25% in compare to control group {*American Academy of Neurology Annual Meeting in Miami , Florida , USA : 9-16 April, 2005*}. Erythropoetin reduces oedema level and the number of inflammatory cells around hematoma [190] and improves cognitive and motor deficits [191].

Free radicals were shown to be a marker of stress process, as they have been found to be highly increased in the group of hemorrhagic stroke patients with lethal outcome [187].

High admission of blood glucose is also recognized as a stress-related-response [50].

Many studies report white blood cell count (WBC), C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) to be increased within 24 hours post-ictus in peripheral blood [192–193, 40, 194–197]. WBC within 24 hours was shown to be mainly represented by neutrophil reaction [198], with further slight decrease and increase in macrophages infiltration using enhancing media, USPIO.

Hyperthermia in patients usually is attributes to cytokine-related increase of hypothalamic set point. Few studies demonstrated that damaging the hypothalamic region causes hyperthermia, thus suggesting that during hemorrhagic stroke the hematoma itself may influence the temperature regulation by compressing hypothalamus and suggesting that hyperthermia may contribute into secondary brain injury [199]. However, study performed by [200] reported that mild and moderate hyperthermia doesn't worsen an outcome after hemorrhagic stroke and is present in cases with small intracerebral haemorrhage, suggesting absence of compressing hypothalamus processes. Taking into account that hemorrhagic stroke resolution is realized through mechanisms of inflammation, it is more accurate to talk about fever in respect of an increase in temperature levels [201–202]. Hypothermia did not show to be of benefit either in the conditions of hemorrhagic stroke [203].

Schwarz et al. reported fever in 91% of observed hemorrhagic stroke patient cases within 72 hours, later Deogaonkar et al. reported fever in 56% of observed hemorrhagic stroke in patient cases within 24 hours, assuming fever development as a condition that accompanies hemorrhagic stroke process [204–205].

Fever that develops in patients with hemorrhagic stroke is represented by leukocytosis [49], the activity and release of the pyrogens, substances produced by granulocytes which induce rapid and brief fevers [206], and mononuclear phagocytes which usually induce prolonged fevers [207]. Pyrogens were also play role in central hyperthermia, when [208] have shown the hypothalamic sensitivity to leukocytes pyrogens.

Fingas et al. found no difference in outcome and functional recovery in rats with selective hypothermia to hyperthermia [209], indirectly suggesting that an increase in temperature in the

conditions of ICH is one of the mechanisms of inflammatory response. Hypothermia was also shown to affect immune system response by reduced number of peripheral lymphocytes and depression of NK cell activity [210].

It is obvious that system level of inflammation is very important in the course and outcomes of the hemorrhagic stroke [154, 48]. However there are still no data what changes in the system level of inflammation provide optimal and best from possible outcomes.

Hemorrhagic stroke complications

Most of the complications of the hemorrhagic stroke are represented by outcome of the disease, and which is in most cases evaluated by the death and the level of functionnal loss post-ictus.

Hemorrhagic stroke complications can be divided into the period of hemorrhage and period of inflammation. Understanding mechanisms of hemorrhagic stroke process and its resolution via inflammation assumes the later to be considered to be of extreme importance. Correlation between hemorrhagic stroke outcome and inflammatory response should be realized both with local and systemic levels.

Taking into account the aim of the article we will discuss some of the hemorrhagic period complications and concentrate more on the complications of inflammation period.

Talking about hemorrhage period in some cases bleeding continue up to 24 hours after the rupture of the vessel. Blood rupture and blood leak trigger a lot of the reflexive regulatory mechanisms and one of them is coagulation cascade, which contributes to the clot formation and leak stop. However, overreaction of the coagulation system may lead to the thrombosis formation, thus the anticoagulation was suggested to be used in patients with high risk of thromboembolism [211]. Later studies showed that use of anticoagulants led to the increase in mortality rate in the treatment group comparing to non-treatment group [212–214]. From these studies we may conclude that medication-induced hypocoagulation led to the enlargement of hematoma and enforcement of all subsequent processes. These complications resulted in 52% the conditions not compatible with life, and, most probably, larger areas involved and bigger functional loss in group of survivals.

There are no studies done that would examine the role of inflammation disorders in terms of hemorrhagic stroke complications. However there are few publications that indirectly show its' relation.

Hyperreactivity of inflammatory response may lead to complications of the hemorrhagic stroke process. For example, some studies have connected molecular markers, such as TNF-α, IL-6 and MMP-9, with subsequent enlargement of the hematoma and risk of recurrent stroke, suggesting that overreaction may lead to the worsen of outcomes [215–217].

Nakai et al. have described post-intracerebral hemorrhage abscess formation with episodes of high fever [218], what may be related to hyperreactive distress and high neutronphilic reaction with prevalence of destructive processes.

The importance of hyporeactivity processes of inflammatory reaction can be found in study done by Qu et al, when they reported chronic expanding encapsulated intracerebral hematoma, suggesting surgical evacuation [219]. One of the mechanisms of its formation could be hyporeactive acute stage of inflammation with low levels of neutrophilic reaction, what led to encapsulation of hematoma without its substitution with neuroglia tissue. One of the possible outcomes for incapsulated hematoma could be cyst formation [220–221].

Other studies give us a chance to conclude that both hyper- and hyporeactivity of system levels badly affect hemorrhagic stroke process. As it was shown, day 1 cortisol levels were associated with 28-days and 1-year mortality. Both high and low levels of circulating cortisol were associated with increased mortality (Abnormal cortisol levels linked to increased mortality J Intern Med 2004; 256: 15-21) [222]. Gapon et al. correlated severity of stroke with serum level of antibodies to differentiation factor [223]. In study of 186 primary hemorrhagic stroke cases the white blood cells count have been performed, suggesting the leukocytosis to be one of the parameters of its bad prognosis [38]. However the prognoses have not been based on the correlation to quantity of leukocytes. Another study done by [49] showed correlation between high leukocytosis level and the mortality, suggesting that overreaction of leukocytes response is harmful, still showing presence of certain level of leukocytosis in a good-outcome group. We suggest that too high and too low leukocytosis both may result in bad outcome of the patients with hemorrhagic stroke, and that the rate of leukocytosis should be just at the level as it needed.

Yoshimoto et al. showed that systemic inflammatory response syndrome was associated with extent of tissue damage at onset and predicted further tissue disruption, producing clinical worsening and, ultimately, a poor outcome [224], however it wasn't taking into account the rate of activity of the response.

Despite there were no studies done that

would examine the role of complications of inflammation, mentioned works above prove its importance and actuality.

Medical interventions into post intracerebral hemorrhage inflammation

Understanding of inflammation as a mechanism that resolves intracerebral hemorrhage led to few approaches of improvement of hemorrhagic stroke outcomes. Unfortunately these studies have not been associated with characteristics of inflammatory process (normal, complicated), thus they couldn't result in defined conclusions [225–228].

More of that, most of studies analyze medical treatment only in the early stages of hemorrhagic stroke without evaluation of the consequences and outcomes. Wasserman et al. have demonstrated that anti-inflammatory action of the minocycline was effective in reduction of TNFalpha and MMP-12 levels in early period and was decreased in a one-week-time [137, 229]. Sinn et al. suggested bortezomib to be used in early stages of hemorrhagic stroke as it was shown that the drug reduces mRNA expression of TNF-alpha, IL-6, iNOS, COX2 levels in first 72 hours post-ictus [230]. Similar study performed by Nagatsuna et al. suggested argatroban to be effective in first 72 hours post intracerebral hemorrhage in reducing of secondary brain damage [231]. The same approach we can find in the works about interventions into ROS production which are evaluated within 24 hours only [232, 99].

It is obvious that achievement of certain aims should be accompanied with obligatory improvement of hemorrhagic stroke outcomes.

CONCLUSION

Despite the fact that hemorrhagic stroke occupies 20% of all stroke cases it still remains one of the most severe and less studied type. Last decades have brought understanding that most of the studies done before in the pathogenesis and treatment hemorrhagic stroke remain controversial and have not brought effective approaches in its diagnostics and treatment.

Later publications suggest that hemorrhagic stroke approaches have shifted towards inflammation theory of the process. However, they in most of the cases present only certain chosen stages of inflammation. Some of publiccations have pointed out the correlation between inflammatory processes disorders and violations with unfavourable hemorrhagic stroke outcomes.

Thus more studies should be done regarding mechanisms of optimal (normal) inflammation development and its disorders in hemorrhagic stroke conditions, what would favour further development of diagnostics and treatment approaches aimed to restoring of its optimality and clinical outcomes.

In this respect experimental neurology remains of extreme importance in its coordination with clinical practice.

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