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New directions in treatment of the ischemic stroke

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1. Abstract

Stroke remains a leading cause of death and disability worldwide. The cause is decrease or total blocking of blood perfusion in brain and fast recognition is essential to conduct proper treatment. Currently commonly used methods are thrombolysis and mechanical thrombectomy, which high efficacy is observed only if they are performed within a few hours of the first symptoms. Hence loads of people, who are diagnosed later, become unable to undergo effective treatment.

In the study are presented pathogenesis, epidemiology, classification, diagnosis and current treatment of the disease, but the main aim of the study is to present the results of the reports on new treatments for ischemic stroke. The research method is a review of the available literature published in PubMed, UpToDate and Google scholar databases.

In the study were reviewed new methods, which can be alternative for currently used ones. They are small molecules including fluoxetine, aripiprazole, L-DOPA, cholinergic and

noradrenergic drugs, growth factors (HCG, EPO), monoclonal antibodies, allogenic stem cells, neurostimulators, robotic therapy and telerehabilitation.
They give hope for curing a larger number of patients and improving effects of rehabilitation after ischemic stroke. However most of the methods, which are presented in this study require the use of tests that will allow checking their safety and application.

Key words: ischemic stroke; thrombolysis; thrombectomy; growth factors; brain stimulation

2. Introduction

2.1. Pathogenesis

The cause of ischemic stroke is decrease or total blocking of blood perfusion in brain. What is interesting, not only stenosis or occlusion may lead to that but also decreased systemic perfusion [1]. Thrombosis and embolism are the most common reasons of changes in blood vessels diameter leading to perfusion disorders. Thrombosis may affects extra cranial as well as intra cranial. Its course may be gradual or acute. In most cases it develops on the basis of atherosclerosis, although sometimes the only reason is hypercoagulability. As atherosclerosis gradually develops, the diameter of vessel decreases and blood perfusion reduces. A blood clot that forms on a ulcerated or ruptured plaque can result in complete acute occlusion of the artery. In most cases the embolic material is thrombus, which settles in the brain vessels, causing their blockage and obstruction [1]. Most frequently it comes from the left heart cavities [2], but arterial vessels may also be its source – artery to artery embolism [1]. Atrial fibrillation is an meaningful disease increasing the risk of ischemic stroke in the mechanism of embolism [3]. In rare cases, the embolus may be cancer cells, fat or air. The cause of air embolism can be, for example, the release of nitrogen bubbles in the systemic circulation as a result of an acute decrease in external pressure. The described situation is known in the nomenclature as a caisson disease and affects divers during ascent too quickly [4]. A decrease in systemic perfusion pressure can cause generalized cerebral ischemia. The reason for this is a significant decrease in blood pressure, heart failure or sudden blood loss [1]. A different pathogenic unit is sinus stroke, which occurs as a result of microcirculation disorders known as small vessel disease. A less common cause of stenosis may be inflammatory processes within the vessels, such as syphilis or collagenosis [5,6]. Stenosis or occlusion of one of the brain or cerebral arteries cause a decrease in regional blood flow and at the level of microcirculation process of molecular changes begins. As a result, neurons and glial cells die. Within 5 minutes of oxygen deprivation irreversible damage of brain tissue occurs [8]. Initially, the decrease in perfusion could be effectively compensated by the action of autoregulatory mechanisms leading to an increase in circulating blood volume. When the artery occlusion occurs suddenly and the collateral circulation is not developed so as to ensure effective perfusion, the symptoms of ischemia appear. The correct value of brain flow is 50 - 55 ml / 100g brain tissue / min [9]. As it decreases, oxygen extraction from hemoglobin increases. When the flow reaches lower values than 20 ml / 100 g brain tissue / min, cellular metabolism switches to anaerobic. As a result the production of lactate and hydrogen ions (H +) increases. Further decrease causes inhibition of the sodium potassium pump (Na + / K + - ATPase) and development of cytotoxic edema. Below the value of 10ml / 100g / the pathways leading to death cell are activated, in which calcium ions (Ca2 +) and glutamate are main

mediators [10]. Electrophysiological changes in neurons lead to an increase in the release of glutamate, which activates NMDA, AMPA and metabotropic receptors, which in turn leads to an outflow of potassium (K +) ions and an inflow of calcium (Ca2 +) and sodium (Na +). During ischemia, there is also an increased formation of reactive oxygen species that damage cellular structures [2]. Cell damage and necrosis trigger an inflammatory response, resulting in l leukocyte migration and cytokine release [11]. The area surrounding necrotic tissue is called penumbra. This is the sphere where the perfusion pressure is decreased and there are changes in metabolic activity of neurons, however these state is potentially reversible. Due to the fast implementation of thrombolytic therapy, it is possible to restore perfusion in this area and inhibit the necrosis process [2]. Risk factors for ischemic stroke are divided into non-modifiable and modifiable. Non-modifiable factors include age, gender, ethnic group and family history. Otherwise the factors which could be modified are hypertension, diabetes, heart disease, in particular atrial fibrillation and a history of myocardial infarction, lipid disorders, obesity, nicotinism, alcohol abuse, low physical activity and a transient ischemic attack [12].

2.2. Epidemiology

Stroke remains one of the main causes of mortality, with ischemic type on the leading position [13]. The victims are more often women, what is probably caused by the fact that their life expectancy is higher than men, which makes them more susceptible to the risk of death associated with age [14]. It was also observed that more often the disease is diagnosed in women who had their first menstrual period before 10 or after 17 years of age, as well as those whose menopause began before 45 years of age [14].

Studies show that the incidence in men has decreased, while in women it remains at the same level [15]. Ischemic stroke is also much more often the cause of death in people over 65, and the risk doubles with every decade after the age of 55 [15,16]. Cases of strokes also occur in children, but more often they are caused by hemorrhage and are most often diagnosed between 2 and 5 years of age [15,16].

As was observed between 1990 and 2016, there was an increase in the global risk of stroke from 22.8% to 24.9% [14].

2.3. Classification and diagnosis

According to American Stroke Association (ASA), a division of the American Heart Association (AHA), there are various types of stroke. The most common – ischemic stroke (87% of all strokes) occurs when there is an obstruction in a blood vessel supplying blood to the brain. The second most frequent one is a hemorrhagic stroke, caused by a rupture of blood vessel, usually due to high blood pressure. Other types are transient ischemic attack (TIA), cryptogenic stroke and brain stem stroke. Only accurate diagnosis of the type of the stroke enables conducting correct treatment. There are many stroke classification systems described. FAST is an acronym used to help to detect the three most common symptoms of stroke. It stands for Facial palsy, any failure of Arm or Speech function and time (to call for help). A stroke is recognized, if at least one of those symptoms occurs [17]. The National Institutes of Health Stroke Scale (NIHSS) is mainly used with acute ischemic stroke [18]. It is a tool to predict the stroke outcome, sometimes used to judge whether to qualify a patient for thrombolysis treatment or not [19]. The most commonly used version is a 15 item scale,

though a few different ones have been created [20]. NIHSS measures patients' consciousness, eye contact, facial palsy, arms and legs strength, ataxia, sensory impairment, aphasia, dysarthria and inattention [18]. What is worth mentioning, NIHSS is a quick test with no special equipment needed and is routinely used in hospitals. Nowadays, the most commonly used system to classify ischemic stroke is the TOAST (Trial of ORG 10172 in acute stroke treatment) created in 1993 [21]. It is composed of five subtypes on the basis of the mechanism that induced the stroke. The subtypes are: large artery atherosclerosis, cardioembolism, small artery occlusion (SAO), stroke of other determined cause and stroke of undetermined cause (SUC) [22]. The particular category indicates the treatment and is noted to influence future prognosis and risk of recurrence. In spite of being a logic and simple system, it has some limitation as well. SAO subtype only includes patients, whose stroke was caused by an infarct of the size of 15mm or smaller [23]. All bigger infarcts are classified into 'undetermined cause' group, although the majority of patients has classic symptoms of artery occlusion [24]. Those conventional criteria are one of the reasons, that about 40% of patients [23] are qualified as cause undetermined [25]. Ten years after the creation of TOAST, Causative Creation System (CSS) was introduced. The need for a more suitable system was due to new diagnostic technology. Just like the previously described categorization, CSS divides stroke into five groups: supra-aortic large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes and undetermined causes. However, the definition of a lesion has been revised and here it includes infarcts up to 20mm diameter. Though being based on TOAST, the CSS system fits the progress better – it integrates the results of various imaging techniques such as diffusion-weighted MRI, CT angiography, echocardiography, ECG and Holter monitoring [23,25]. ASCO (atherosclerosis, small-vessel disease, cardiac source, other cause) is a phenotypic-oriented system, created in 2009. It divides patients relying not only on etiology of the stroke, but also co-existing diseases. They are qualified on the basis of likelihood of each of the four potential causes of the stroke. ASCO has enabled to decrease the number of patients qualified with „unknown cause of ischemic stroke" [25]. Another classification is OCSP (Oxfordshire Community Stroke Project Classification) from 1991. It is a clinical tool based on the symptoms reported by patients. Accordingly, we can predict the course of the disease and the likelihood of stroke recurrence. OCSP classifies stroke into four categories: total anterior circulation infarct, partial anterior circulation infarct, posterior circulation infarct and lacunar syndrome [26].

2.4. Current treatment

Nowadays, we have two basic methods of management acute ischemic stroke which are being used in daily practice. The aim of this part of article is to show recent reports of their effectiveness. There are many research on acute ischemic stroke. Some of the studies bring a lot into modern neurology. First, main method is intravenous thrombolysis. In case of acute ischemic stroke a recommended drug is alteplase (dose a 0.9 mg/kg). Chen's meta-analysis reports: "alteplase within 3 hours should be recommended as the best treatment delay for its best efficacy among all the intervention and equivalent safety compared with placebo" [27]. Discussion about a time window from stroke to treatment using alteplase presents that, "using it beyond 3 hours was less effective compared with that within 3 hours". They observed that it enhanced the risk of mortality on 3 months and that was associated with symptomatic

intracerebral haemorrhage at 36 hours. Taking into account SUCRA (Surface Under the Cumulative Ranking Curve) rate for used alteplase within 3 hours after acute ischemic stroke – "occurrence (SUCRA=98.3%) was significantly more effective (OR=1.64) than that at 3–4.5 hours (SUCRA=43%)". The treatment beyond 4.5 hours was a bit worse (OR=1.47) (SUCRA=58%) but of course also many patients recovered. Also mortality is correlated with time of treatment for stroke. "Alteplase within 3 hours was equally to that of 3–4.5 hours whereas alteplase beyond 4.5 hours (SUCRA=7.3%) showed the trend of visibly enhancing 85% mortality.".

According to the Polish Neurological Society intravenous alteplase is recommended for patients within 4,5 hours after acute ischemic stroke. On the basis of individual patient data from randomised trials the WAKE-UP trial demonstrated the advantage of intravenous thrombolysis with alteplase in patients with stroke symptoms on waking by identifying an MRI (Magnetic Resonance Imaging) pattern suggestive of stroke with an onset of less than 4,5 h [28]. On the other hand we need to take into account the group of patients who are in a few percent of patients having benefits from alteplase treatment despite being beyond 4,5 hours. Another meta-analysis is showing the usage of thrombolysis with intravenous alteplase in patients with acute ischemic stroke 4,5–9 h after stroke onset or wake-up stroke. There was a need to identify patients with salvageable brain tissue who could be treated beyond time window. This group of patients was imaged with CT (Computer Tomography) perfusion or perfusion-diffusion MRI, and showed functional outcomes compared with placebo [29]. They achieved advantages with alteplase treatment. In spite of that success, "the frequency of symptomatic intracerebral haemorrhage was around 4% higher in the alteplase group than the placebo group, which is consistent with the results of previous trials of alteplase 0–4,5 h after stroke.". The second method being used is endovascular thrombectomy. This method should be a standard treatment of patients with acute ischemic stroke, but still is not commonly used. Meta-analysis showed existing visible distinguish of mortality in acute ischemic stroke between regions; it was connected with not using that method in treatment. The other meta-analysis described effectiveness of endovascular thrombectomy over standard medical care in patients with acute ischemic stroke caused by occlusion in anterior circulation. It reports: "endovascular thrombectomy led to significantly reduced disability at 90 days compared with control (adjusted cOR 2·49, 95% CI 1·76–3·53; p<0·0001)."[30]. Endovascular thrombectomy is of benefit to most patients with acute ischemic stroke, regardless of patient features or geographical location. However, slightly fewer patients in the intervention group were treated with intravenous alteplase before randomisation (p=0·04) so it is not clear if only thrombectomy is helpful like in previous results or combination of these two methods [30]. General problem of management in patients with acute ischemic stroke is time to treat them in a way which would be most beneficial for them. The Polish Neurological Society recommend endovascular thrombectomy for patients within 6 hours after acute ischemic stroke.

3. Methods and aim of the work

The aim of the study is to present the latest reports on the new directions in treatment of ischemic stroke.

The research method is a review of the available literature found in the PubMed, UpToDate and Google scholar databases.

4. New directions in treatment

4.1. Small molecules

In the past few years interest in small molecules therapy has increased. Fluoxetine, Serotonin Selective Reuptake Inhibitor (SSRI), given for three months after the stroke, can improve patients' neurological functions [31]. This well known anti-depression drug is estimated to reduce dependency, disability and neurological impairment in post-stroke patients [32, 33]. Dopamine regulates many aspects in neuronal system such as synaptic transmission and gene transcription [34]. It also has a beneficial role in post-stroke recovery. Aripiprazole, a partial D2 receptor agonist, improves remodeling of neuronal cells, while blockers of dopamine receptors (e.g. haloperidol) inhibits the regeneration [35]. The results of administrating L-DOPA for 6 months after the stroke were significantly better in terms of motor recovery compared to placebo group [35]. Cholinergic and noradrenergic drugs may also have favorable effects on treating patients after stroke, though more studies are needed to confirm the issue [35].

4.2. Growth factors

Growth factors levels increase spontaneously after the stroke. They are responsible for neuronal development, synapse formation, angiogenesis and other repair mechanisms [33]. According to the recent studies, supplementation of growth factors can prevent post-stroke cognitive impairment [36]. Influence of human chorionic gonadotropin (HCG) and erythropoietin (EPO) – hormones that cross blood-brain barrier - was evaluated in several researches. Exogenous administration of bHCG stimulates proliferation of neural stem cell and erythropoietin promotes their differentiation into neurons. Combined treatment with those two growth factors can significantly diminish the volume of lesions in preclinical studies [37]. Despite the fact, that there is a high probability that growth factors would have comparable effects in humans, further studies are necessary [33].

4.3. Monoclonal bodies

Monoclonal antibodies, also known as monoclonal immunoglobulins, are antibodies made by immune B-cells that are all clones. By binding to the antigen they can directly modulate the cell, while their indirect influence involves recruitment of effector cells such as macrophages and natural killer cells [38]. An increase of inhibitors (myelin-associated glycoprotein, oligo-associated glycoprotein, ephrin A5, chondroitin sulfate proteoglycans, neurite outgrowth inhibitor-A) is observed after the stroke [33, 39]. The aim of monoclonal antibodies is neutralization of these inhibitors to restore an adequate molecular-profile in post-stroke brain [39]. There are several reports suggesting efficacy of monoclonal antibodies in post-stroke treatment. A positive influence of monoclonal antibodies administration in gain recovery, behaviour and natural-lasticity was observed [33, 40]. However, they are mostly animal-based

or small research group trials, therefore further clinical studies are indispensable to gain evidence that the therapy is effective in human population [40].

4.4. Cellular therapy

Cell therapy has a multidirectional effect on brain nerve tissue after a stroke. Transplanted cells have the ability to integrate into tissue architecture and replace neurons that have died as a result of stroke. These cells also secrete cytokines, growth factors and extracellular matrix proteins, and also modify the systemic immune response, which promotes the regeneration of nerve tissue. [33] Allogeneic stem cells derived from bone marrow [41], neural stem cells [42], mesenchymal stem cells [43], embryonic stem cells and induced pluripotent stem cells [44] are used in this therapy. Studies carried out so far show that cell therapy used both systemically and intracranial is safe and brings good results in the treatment of early and late changes occurring after stroke [33]. The development of guidelines for a treatment plan as well as appropriate dosages require further studies.

4.5. Brain stimulation

There were published independent results of clinical trials connected with brain stimulation as a new method in acute ischemic stroke therapy, some of them aimed at increasing, and some at reducing brain activity [33]. In 2019, Bornstein N. M., Saver J. L., et al. revealed results of shame-controlled, pivotal and double-blind study, which was done in 73 centers in 18 countries. It involved 1078 patients (481 received stimulation of sphenopalatine ganglion), both women and men, aged between 40-85 years. The neurostimulating implant was injected near pterygopalatine ganglion, and after that patients were undertaken five sessions, each day for four hours. As it was observed, it is safe therapy for patients with acute ischemic stroke, who were not classified to actual treatment, diagnosed between 8 and 24 hours after showing of outcomes and it can improve patients' activity. Now we have loads of hypothesis associated with beneficial effects of this therapy (increase in blood flow, neuronal recovery), but there is still a need of further studies, which may help with fitting the best doses, intensity and technical procedures to brighten effects of the method [45].

4.6. Robotics

Promising results in the rehabilitation of stroke patients may bring the use of robots. Their advantage is definitely the fact that they can be programmed according to the needs of a specific group of patients. So far, numerous robotic systems have been investigated [46], but the conclusions from the current research are not clear. In a multicentre study conducted in 2010 on a group of 127 patients, it was shown that 12 weeks of robotic rehabilitation did not significantly improve motor function compared to standard care or intensive care. However, in a study performed after 36 weeks, there were observed better effects of robotic therapy compared to standard care [47]. In a randomized study conducted on a group of 21 patients after stroke with paresis of the upper limb, a comparable improvement of motor function in robot therapy and physiotherapy was obtained [48,49]. The economic benefits of using this therapy are also worth emphasis, however, compared to standard physiotherapeutic methods, robotic therapy requires higher costs [50]. Phase 2 and 3 studies are still needed to extract the

group of patients who benefit most from robotic rehabilitation and to develop therapies based on maximizing the benefits of robotic system [1].

4.7. Brain computer interfaces

A brain-computer interface (BCI) gives a chance for people to transmit information without moving. It is based on the fact that computer can detect patients' mental activities, such as imagining movement or counting flashes. Afterwards the computer provides a real-time feedback. For example, BCI can be used to help people with ischemic stroke regain movement. It also enables patients to communicate with environment [51]. Rehabilitation after stroke requires active movement, unfortunately some of patient with spasticity can not do volitional movements to train the affected side. Brain-computer interface connected with virtual reality like the the new REINVENT architecture allowed the patient to be learning to modulate his own motor brain activity The research with REINVENT architecture lasted for 16 sessions. It has shown that training is feasible to use for individuals with chronic severe stroke [52]. Worthily to note that, Virtual reality (VR) is a computer-based technology that allows patients to interact with a multisensory simulated environment. So it provides the stimuli to the brain and raises its activity.

4.8. Telerehabilitation

Telerehabilitation is a new method that has brought a broad group of patients the possibility of rehabilitation. It is important especially in the small villages and in the poor countries, where the rate of stroke is still rising. Rehabilitation after stroke requires the inputs of several skilled health personnel, including physiatrists, physiotherapists, speech therapists, and occupational therapists. After analysis of researches it can be claimed that tele-rehabilitation interventions were associated with significant improvements in recovery from motor deficits, higher cortical dysfunction, and depression in the intervention groups in all studies [53].

5. Summary

New methods give a chance to cure patients who were previously disqualified for treatment with currently used methods, due to the time criterion. In addition, some of them enable patients to achieve a higher quality of life after treatment than those who are receiving treatment with current procedures. However, further research is needed to determine the effectiveness and safety of new methods.

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