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Review Articles

Stroke – Some Risk Factors, Neuropathological Aspects and Neurorehabilitation Approaches

Dimitar Maslarov[1,2], Desislava Drenska[1], Iskra Sainova[3], Vera Kolyovska[3]*

[1] University First MHAT-Sofia, "St. John Krastitel", Neurology Clinic, Sofia, Bulgaria
[2] Medical University of Sofia, Medical College "Y. Filaretova", Sofia, Bulgaria
[3] Institute of Experimental Morphology, Pathology and Anthropology with Museum, Bulgarian Academy of Sciences, Sofia, Bulgaria

*Corresponding author e-mail: verakol@abv.bg

In many cases the stroke is fatal, in other patients various types and degrees of disability are available, most often affecting the cognitive, motor and perceptive functions. Some vascular and circulation diversions concerning the function of the central nervous system may result in parenchymal lesions that could be hemorrhagic, ischemic or mixed. Modifiable risk factors are hypertonia, metabolic syndrome, changes in blood coagulation status, etc. Non-modifiable are age, gender, race and genetic predisposition. Consequences of the stroke could affect different motor and/or cognitive functions. Stroke rehabilitation includes any procedure that aims to facilitate the optimal functioning of individuals experiencing or likely to have post-stroke difficulties in interacting with their environment. Neurorehabilitation after stroke is based on neurorecovery, neuroplasticity and neuroregeneration. The main goals are directed to prevention and reduction the severity of stroke, death risk and long-term consequences. Development of interdisciplinary social programs is necessary. Elimination of the risk factors would be the best prophylactic.

Key words: stroke, neuropathological aspects, risk factors, cognitive rehabilitation, robotic rehabilitation

Introduction

According to statistics, every minute one person in the European Union suffers a stroke. Strokes can be fatal or debilitating, causing a change in the life of not only the patient but also their loved ones. The number of ischemic strokes in Bulgaria is around 40,000 – 50,000 cases per year and 3,500 patients with non-traumatic cerebral hemorrhages (parenchymal and subarachnoid) [19, 22]. In the recent decades, health systems worldwide have faced increasing challenges:

– increase in healthcare costs;
– shortage and uneven distribution of health professionals at all levels;
– inequality in terms of access to health care;
– aging of the population, which leads to an increase in chronic diseases and polymorbidity.

Four over-arching targets for 2030 have been identified according to "Stroke Action Plan for Europe" (SAP-E) [28]: Creation of a national plan covering the entire chain of stroke care – from primary prevention to life after stroke; Creation and implementation of a national strategy to encourage the population for a healthy lifestyle; Over 90% of stroke patients receive prompt and adequate treatment in a specialized hospital unit that has specialists and equipment; To reduce the number of strokes by 10% [28].

Some risk factors for stroke

Risk factors are divided into two large groups; one group is called non-modifiable which reflects factors without significant difference. These are: age, gender, race and genetic predisposition [19, 22, 29].

The other group are the so-called modifiable risk factors. They can also be divided into two groups – one group are those with known and proven impact and are called "well-documented". The other group are the factors we called "less well documented". It is a combination of several facts that have a great cumulative weight for the occurrence of a stroke. These include: hypertonia, metabolic syndrome, alcohol abuse, hyperhomocysteinemia, hyperuricemia, drug abuse, changes in blood coagulation status, long-term and uncontrolled use of oral contraceptives, severe migraine, obstructive sleep apnea, depression.

Obstructive sleep apnea has recently taken an increasingly prominent place in risk factor commentary and is even expected to move from the group of less well-documented to well-documented risk factors. It has been shown that during some part of the night, the blood in these people is not sufficiently enriched with oxygen. This has an impact on its coagulation qualities and on the oxygen saturation of the neurons, and they need two things – oxygen and glucose, supplied only by the circulating arterial blood [19, 22, 29]. Another recent focus is elevated blood levels of uric acid, which could be related to both increased production and impaired excretion by the kidneys. In the recent years, a group of strokes has been distinguished, called "wake-up strokes", in which we do not have clarity when the initial time of symptom onset is. This limits us in the possibility of carrying out a specific treatment – venous thrombolysis. The main limitation for carrying out this treatment is time – up to four and a half hours from the first signs, or this is the so-called "therapeutic window".

Viruses, including SARS-CoV-2/COVID-19, and other infectious microbes have also been associated with an increased risk for stroke through direct or indirect influence due to long-term complications [22, 33].

Some neuropathological aspects in stroke

Strokes are most often due to thrombus formation, atherosclerosis and hemorrhage (**Fig. 1**, [11]; **Fig. 2**, [14]). Cerebral thrombosis and atherosclerosis are the main cause for ischemic stroke, which accounts for more than 80% of all strokes. Thrombolysis and thrombectomy **(Fig. 3)** [34] may significantly improve functional outcomes after ischemic stroke when performed within the first hours of the onset of symptoms. The type and size of infarcts are often associated with different hemodynamic patterns **(Fig. 4)** [15]. The consequences depend on which part of the brain is affected, the severity and duration of ischemia. The hippocampus, neocortex, striatum and the cerebellar cortex are the brain regions with the highest ischemic vulnerability [15].

Stroke neuropathology is associated with brain swelling, edema, blood-brain barrier breakdown and inflammation. The most sensitive cell types within the brain are the neurons, followed by oligodendrocytes, astrocytes and vascular cells [15]. Histopathological characteristics of the infarct brain areas include neuronal necrosis, reactive astrogliosis and activated microglia [10]. Endothelial dysfunction (including tight junction disruption and loss of barrier properties), contributes to parenchymal damage and neurological deficits [2]. Pathophysiological disturbances of microcirculation in stroke disrupt the neuron-microvascular interactions in the "neurovascular unit", which consists of microvessel components (endothelial cells, basal lamina matrix, astrocytic endfeet, pericytes), astrocytes, the nearby neurons and their axons and supporting cells (microglia and oligodendrocytes) [15]. Targeting the "neurovascular unit" may have beneficial effect against deleterious outcomes following an ischemic stroke.

Strategies for prevention of stroke

Primary prevention of stroke includes prevention of atherosclerosis in general, because it is a major risk factor for damage to cerebral vessels. Changing people's behavior and completely eliminating risk factors such as smoking, unhealthy eating, alcohol use, etc., would be the best choice to reduce the risk of the diseases associated with them. However, experience shows that this is not possible in most cases. As we already mentioned, these risk factors are often in combination and their negative effect aggregates. When we discuss physical activity, we mean that it should be regular, non-exhausting and systematic. Therefore applications for smartphones have been developed that allow a person to plan his route by walking 10 000 steps a day which has a beneficial effect on the overall physiology of the body and on brain function.

Recognizing transient ischemic attacks is the moment when we must act actively. We must assess the patient's condition and focus on what exactly needs to be added to the therapy, what to change in his/her diet and lifestyle, so that a second similar or more severe incident does not occur - that is known as personalized medicine. This action of ours is called secondary prevention. The development of telemedicine at the present time is of great benefit to us [19,22].

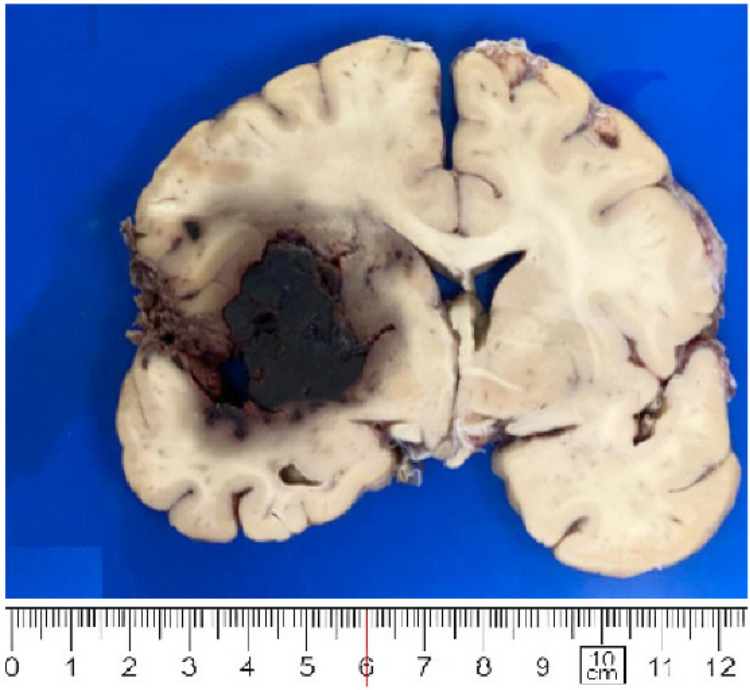

Fig.1. Large hemorrhage in basal ganglia [11].

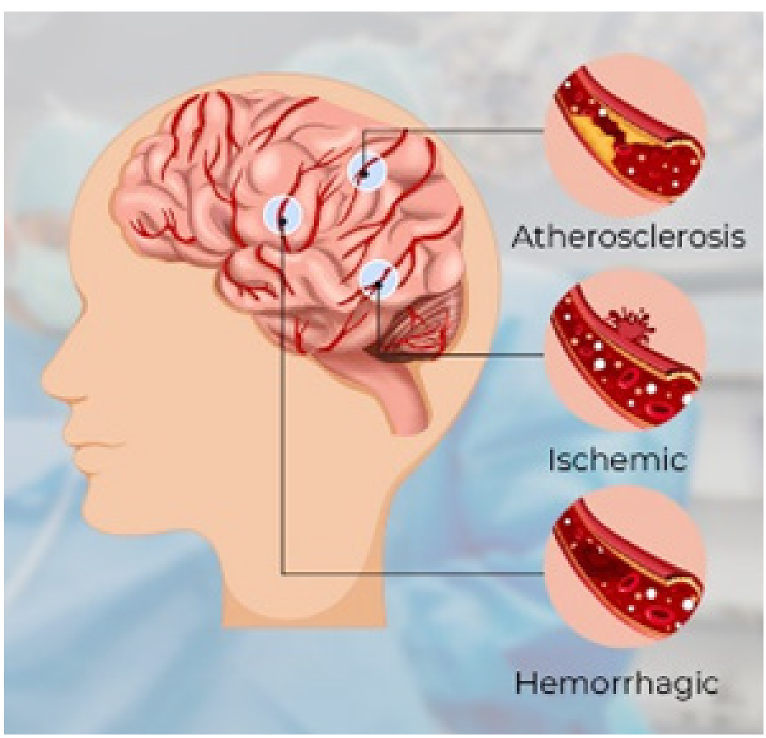

Fig. 2. Types of stroke [14].

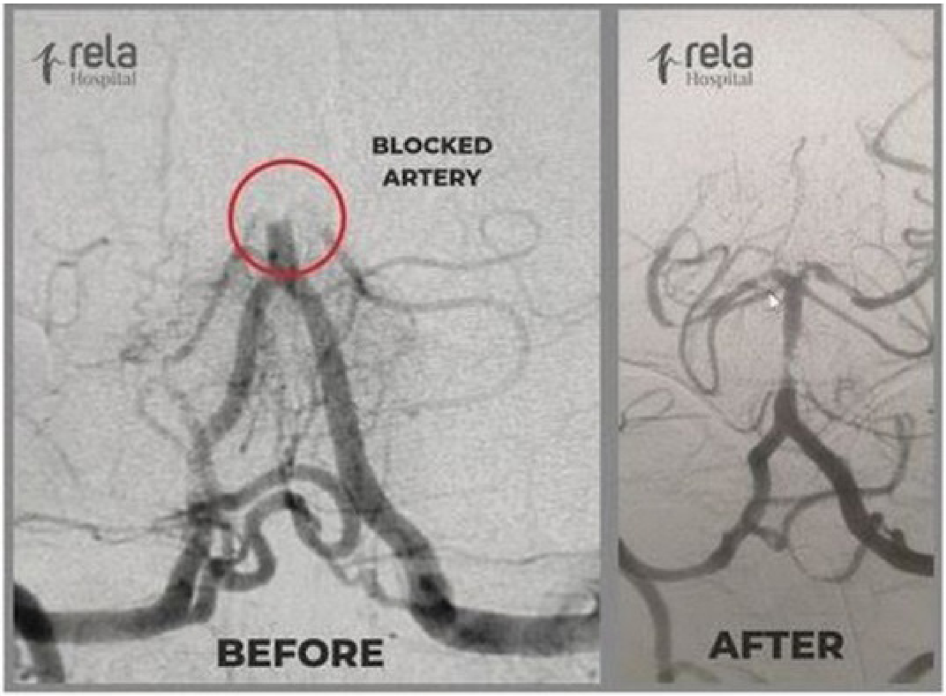

Fig. 3. Mechanical Thrombectomy [34].

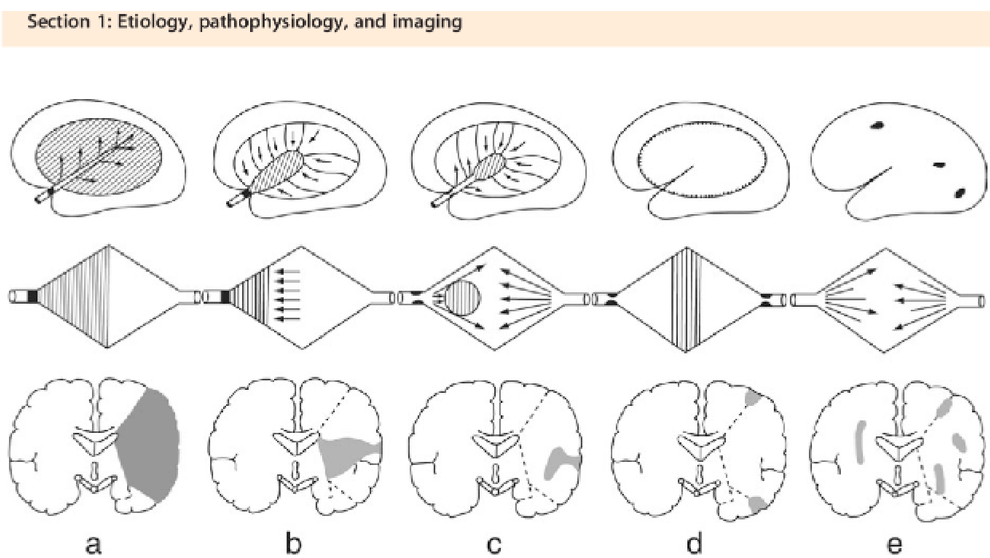

Fig. 4. Various types and sizes of infarcts due to different hemodynamic patterns: a. Total territorial infarct due to defective collateral supply. b. Core infarct, meningeal anastomosis supply peripheral zones. c. Territorial infarct in center of supply area, due to branch occlusion. d. Borderzone infarction in watershed areas due to stenotic lesions in arteries supplying neighboring areas. e. Lacunar infarctions due to small-vessel disease [15].

Neurorehabilitation after stroke

The pharmacologic intervention for early motor rehabilitation after acute ischemic stroke should always be complement (not compete with) neurorehabilitation programs and the initiation of treatment should occur within 7-day window after stroke to enhance endogenous plasticity, consistent with the definitions and shared vision for new standards of stroke recovery research [19, 30].

Stroke rehabilitation includes any procedure that aims to facilitate the optimal functioning of individuals experiencing or likely to have post-stroke difficulties in interacting with their environment. Neurorecovery is a dynamic and multifactorial process and occurs most actively during the first 30 days after stroke onset [22, 24]. Neuroplasticity is a process of biological support for brain recovery, including all mechanisms of neuronal reorganization, including synaptogenesis, dendritic growth, axonal sprouting, the establishment of new anatomical pathways with similar functions to damaged ones, activation of functional but silent synapses, and cell genesis [25]. These metabolic, inflammatory and genetic processes occur in a specific temporal sequence, depending on the time elapsed since the onset of the stroke.

A thorough understanding of the sequence and interrelationships between these processes is vital, as various pharmacological or non-pharmacological therapies have the potential to reduce disability only if applied at the right time. Pharmacological intervention can overcome inhibitory mechanisms and stimulate neuroplasticity in many ways ranging from behavior to gene expression [13, 26]. Neuronal plasticity is at the core of functional recovery after stroke, and it is important to develop robust strategies to facilitate this process in order to offer the best treatment for stroke patients.

In the last years the information, received by the people all over the world by Internet, including the approach to a social net in each separate moment, has significantly increased. By taking in consideration the recommendations of the World Neurology Federation, World Stroke Federation, etc., the mobile application Stroke Riskometer has been developed. Its main goal is related with possibility about a better determination of the individual risk of eventual stroke for a 5-10 years period, which could give directions about decrease and prevention of this risk.

The advantages of computer programs for cognitive rehabilitation compared to classical methods are systematization of the process and the levels of difficulty, fast feedback, the possibility of quantitative assessment and analysis and application in home conditions [6];

– training and recovery of daily routine activities of the patient, which is important to recover up to a year after the stroke;

– although the evidence for the benefit of rehabilitative interventions after the first year of illness is scarce, it is important to know that improvement can continue long after the stroke and patient needs vary over time. Therefore, it is never too late for rehabilitation. If this is not possible, an adequate alternative should be provided for the continued recovery of the patient.

<u>*Cognitive rehabilitation.*</u> Studies show that up to 13% of patients have mild cognitive impairment before the onset of stroke, and 10 to 15% have pre-existing dementia. After the first cerebrovascular accident, approximately 30% have varying

degrees of cognitive impairment, and 10% have a more severe form of cognitive impairment – dementia. Over 30% of patients develop dementia as a result of multiple recurrent lacunar strokes [4, 5, 21, 26].

Cognitive neurorehabilitation has 4 main areas of application [17, 18, 23]:

1. Training and guidance – with a focus on developing self-awareness and insight into the problem. Through specialized training, the patient with brain damage aims to become aware of existing problems. This is done through accessible explanations of brain functions, brain areas potentially affected and their effect on daily activities. Awareness of the problem leads to a higher degree of adaptation and adjustment.
2. Learning process - with a recovery focus. The learning process aims to restore cognitive skills that have been lost or impaired as a result of the brain injury. All competencies are included here with the idea of automating actions. Neuronal plasticity enables the creation of new anatomical and functional connections and pathways to redirect information around damaged areas. Through the specific cognitive abilities, the natural processes of neuroregeneration and the set of skills built in the course of training are stimulated.
3. Strategically oriented training - with a focus on compensating the problem during a difficult recovery process. When cognitive skills cannot be restored, training in balancing logistic models is switched. They most often use additional aids such as electronic devices, diaries, notebooks, clocks or alarms. Their correct use creates an opportunity for alternative problem solving and the patient can preserve his independent functioning and quality of life, without an increased level of anxiety and/or depression.
4. Training for functional activities - with a focus on improvement in real life. The ultimate goal of all cognitive rehabilitation programs is better and independent functioning. Emphasis is placed on the performance of tasks of varying difficulty and thus working on a certain cognitive ability, that is, training to perform routine daily activities also contributes to the recovery of premorbid cognitive capacity.

Transcranial magnetic stimulation. Neuronal reorganization after stroke has been observed in functional imaging studies that provide information on changes in stimulus or task-induced activation patterns in the affected and contralateral brain hemispheres [7, 31, 32]. The finding that modifications in network connectivity are relevant to neurological dysfunction has inspired the concept of "correcting" dysfunctional network architecture by using noninvasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) [3, 16].

Mirror therapy. One of the most severe syndromes after a stroke is the "paretic arm". The motor representation of the cortex is impaired in function and due to the lack of movements in the corresponding hand, as sensory deficits limit cortical activation [1]. Rehabilitation strategies should be intensive, repetitive, specifically oriented and directed at endogenous neuroprotective and restorative processes (integral neurogenesis) after stroke. The concept of mirror therapy has a neurophysiological basis. The mirror is placed in the patient's midsagittal plane, presenting the participant with the mirror image of their unaffected arm. By moving the nonparetic upper limb, visual image inversion elicits lateralizing cortical activation [12, 13]. The involvement of different cortical areas in the processes that mediate recovery and the exact mechanism of mirror therapy are still not fully understood. Its effects are often associated with "mirror neurons" in monkey and human premotor areas activated during observation of corresponding movements [8, 9, 29].

Virtual reality. Virtual reality involves specific software-generated actions that are performed by the patient and facilitate the improvement of motor and cognitive impairments. An important advantage is the availability of immediate feedback for the implemented activities of the participant. At the beginning of the implementation and implementation processes, virtual reality was used to test the one-dimensional side of vascular lesions, but over time the experimental paradigm shifted to multimodal peer manifestations and procedures.

Mirror box illusion. The Mirror Box Illusion is one of the most famous cognitive mirror illusions based on visual-motor conflict. While one hand is behind the mirror, hidden from view, participants move the other hand in front of a parasagittal mirror. Possible perceptions are projected onto the hidden limb with the characteristic of symmetrical bimanual movements and other deceptive kinesthetic (kinesthesia - a type of joint-muscle sensation related to displacement in space) and motor effects. Thus, observing one's own actions in the mirror increases excitability in the motor cortex ipsilateral to the moving hand [25].

Rubber hand illusion. Another crossover method is the Rubber Hand Illusion – it consists of moving a brush with soft hair (or a feather) on one of the subject's hands (hidden and invisible to the observer), while at the same time the researcher moves a similar object on an artificial rubber hand located in place of the hidden one. In this way, a sense of ownership of the rubber hand is created in the patient [7]. The principles used are [7, 20]: an increase in proprioceptive function, an altered volume of movements performed with the stimulated arm, and a stronger connection between body representation and the multimodal integration of touch, proprioception, and visual stimuli.

Robotic Therapies (RT)

– Functional electrostimulator (Foot Drop System - FDS) – is an innovative system with many sensors for measuring movement in the paretic limb. The device adapts to the patient – walking speed, foot length, walking symmetry. In the walking phase, the device generates pulses and stimulates dorsiflexion at the required moment. Similar is the interactive hand rehabilitation system, through which passive and active assisted rehabilitation, active assistance and interactive games are carried out [27].

– LEXO® systems enable training towards a physiological walking pattern that, through specific training, strongly engages the patient (initial contact, stance phase, swing phase).

– Lokomat® is another leader in robotic medical devices that support brain function in neurorehabilitation through state-of-the-art gait training - especially for patients with severe and moderate disabilities.

– The SafeGait 360° Balance and Mobility Trainer® is a ceiling mounted dynamic body support and fall protection system. It provides a safe and effective therapy session for people with various disabilities who regain walking, improve their muscle strength and overcome balance problems. SafeGait tracks the patient's movements 2,500 times per second. The state-of-the-art device slides along a monorail, moves and protects patients during their daily therapeutic activities. The system stabilizes the participant's position and ensures constant tension on the support band. In this way, a safe environment and high individual motivation are created, necessary for conducting early and intensive therapy. All performance parameters are documented, including time, distance, repetitions, falls prevented, average body weight support and speed.

– RecoveriX stroke therapy is the first rehabilitation system based on a brain-computer interface that links mental activities (especially movement imagination) with real-time visual and tactile feedback i. e. with motor functions. Patients are instructed to imagine movement of an upper or lower limb. Once the RecoveriX system successfully recognizes the motor imagery, virtual reality and functional electrical stimulation are activated. Patients report feeling warmth in their extremities and a parallel improvement in memory, concentration and language functions.

– The Stiwell system focuses on motor learning in the following known aspects: active activities, goal-oriented and randomized actions, varied exercise options, "basic" daily activities, optimal feedback, task repetition, and maintenance of motivation. The recommended frequency of therapy is 5 exercises of 30-45 minutes per week.

– Biofeedback. Movement disorders can be treated with biofeedback. An electromedical device communicates the movements in person using visual and audio signals and the patient becomes aware and understands their movements. The result is relearning of the motor act and/or conscious maintenance of tension in the affected muscles in existing paralysis. Symptom-oriented biofeedback training is an effective tool and can be combined with muscle-controlled electrotherapy. It is used in the course of rehabilitation or in the form of controlled therapy in outpatient settings [16].

There is significant potential to reduce the severity of stroke, including its long-term consequences. This requires joint and coordinated actions of health professionals from different specialties (mainly neurologists, but also interventional radiologists, physiotherapists, etc.), the pharmaceutical industry, the ministries of health and social policy, other government bodies and non-governmental organizations. It is extremely important to raise the level of literacy of the population regarding the early recognition of the signs of a stroke.

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