NEUROPROTECTORS: NEW OPPORTUNITIES IN THE TREATMENT OF STROKE

In Russia, as in many other countries, stroke is the leading cause of death. Even with a favorable outcome, only 8% of patients are able to return to their previous place of employment and the way of life (!). Timely medical care gives a much greater hope for a favorable outcome of the disease, and the administration of new neuroprotective agents capable of influencing the key points of the ischemic cascade is an essential part of the treatment.We asked a Corresponding Member of RAMS, Director of the Institute of Stroke of RSMU, Head of the Department of Basic and Clinical Neurology and Neurosurgery at RSMU (Russian State Medical University) - Professor **Veronika I. Skvortsova** to tell us about this problem in more detail

- Could you tell us, what place does ischemic stroke have among other diseases? How common is it in our country?

- Over the past 5 years, 6.4 million people died in Russia, of whom 58% died of cardiovascular disease. Cerebral stroke is the second largest cause of overall mortality of our population (23.4%). Among circulatory diseases cerebral stroke has a 39% mortality rate. Annual mortality from stroke in Russia is one of the highest in the world. Moreover, the lethality rate among persons of a working age has increased in the past 10 years by more than 30%. Early 30-day mortality rate after a stroke incident is 34.6%, and within a year - 48% of patients die, i.e. every other patient.

Stroke is the leading cause of disability in the population. According to the National Stroke Registry, 31% of patients who had the disease require outside help, 20% are unable to walk independently. Only 8% of survivors can return to their previous place of employment. Stroke imposes special obligations on family members of patients, significantly reducing their work potential.

- Are there solutions to deal with this problem today?

- The international experience shows that a decrease in mortality of the population from cardiovascular diseases is achieved as a result of a coordinated set of measures. It is necessary to raise awareness in the population (on national and regional levels) of risk factors of vascular diseases and their prevention (promotion of healthy lifestyles). It is also necessary to raise awareness of the early signs of stroke and the appropriate actions to take when they occur. It is necessary to implement effective prevention programs, improve medical care for already occurred stroke (early diagnosis, treatment, secondary prevention, aftercare). The obligatory method of controlling such a global and multiphasic problem is to create a unified national program. This program should be based on a systematic multidisciplinary approach that includes a distinct coordination of all services, agencies and professionals involved in the diagnosis and treatment of stroke, as well as overcoming the fragmentation of medical and economic resources, and problems of coordination between different agencies and disciplines.

- Does this program already exist in Russia?

- At present, Russia is starting an implementation of the federal program, "A set of measures for prevention, diagnosis and treatment of patients suffering from cardiovascular disease" that is aimed at primary prevention of cardiovascular disease, including stroke. It is proven that introduction of primary prevention allows prevention of at least 100 cases of stroke per 100000 people in 3-5 years.

An important component of the program aimed at reduction of mortality from stroke is the organization of primary departments for treatment of acute cerebrovascular events. They will be created on the basis of efficient municipal and regional multi-disciplinary hospitals having neurological, therapeutical, surgical departments, an emergency laboratory and ambulance units in their structures. Primary departments for treatment of stroke should be located in such a way that a patient could be taken to the hospital within 30-40 minutes from anywhere in the region. In addition, they must have high-precision diagnostic equipment (computerized tomography) that would allow them to carry out a differential diagnosis and determine a type of the stroke, and, consequently, to prescribe an adequate treatment. An important component of the program is the early treatment of patients in primary units from the first day of stroke by efforts of a multidisciplinary team. Implementation of the program will allow an increase in the availability and quality of medical care administered to all patients suffering from cerebrovascular pathology. The program will also lead to the use of new technologies in the treatment and prevention of stroke, including minimally invasive neurosurgery, as well as to reduce the death rate from stroke by 15-18%, lethality - by 6-7%, and disability - by 4%.

The program implementation is planned for 2008-2010. Today, more than 20 RF subjects have a high degree of preparedness for the implementation of this program. Staff training and retraining have been started: multidisciplinary teams for primary departments, highly qualified specialists for the regional vascular centers, physicians for primary care and ambulance services.

- Would you describe causes and clinical implications of ischemic stroke?

-Ischemic stroke or cerebral infarction is the most common form of stroke. Its share is about 80% of cases. Ischemic stroke is a clinical syndrome; it appears as result of various diseases: of the heart, blood vessels, blood system, etc. As a result it is possible to observe blood flow disturbances in certain blood vessels and consequently a disrupted blood supply to an area of the brain, where focal ischemia develops. In this regard, there are only two pathogenetic mechanisms of treatment: reperfusion (restoration of blood flow) and cytoprotection (protection of the brain from ischemia).

Specialists know that in stroke there is a so-called therapeutic window, when symptoms have already arrived, but there are still no irreversible pathophysiological changes in the brain. This period of time in most patients is 3-6 hours, when the most effective therapeutic intervention is possible. Unfortunately, in our country only a small percentage of patients get into the hospitals in this period of time due to low awareness in the population of the symptoms of stroke; people often do not attach much importance to appearance of persistent numbness or "clumsiness" when moving limbs, or dizziness.

Therefore, there should be greater awareness in the population about the symptoms of the disease and its consequences.

- How is the treatment conducted, and what drugs are used for therapy?

Thanks to the studies of recent decades, the understanding of the mechanisms of tissue damage, which occurs during acute cerebral ischemia has greatly changed. Among the health practioners, a stroke has been traditionally viewed as an urgent condition that requires quick and pathogenetically substantiated therapy, maximally effective within the therapeutic window. The most effective way of treatment of ischemic stroke is a therapeutic reperfusion strategy using thrombolysis. In Russia, we started implementing this method only in 2005 in the Institute of Stroke of RSMU; today it is used in all large hospitals in the country. However, a modern reperfusion therapy is possible only after a neurovisualising assessment of the stroke nature and type (excluding hemorrhagic component of damage) that is possible only with the proper diagnostic equipment. In addition, thrombolysis has several limitations: association with a concomitant somatic pathology (uncorrectable hyperglycemia or high blood pressure), and the severity of the patient's condition.

In comparison with reperfusion, a neuroprotective therapy has no such restrictions, and allows us to use neuroprotectors in the first minutes of stroke. Early neuroprotective therapy results in the increase in the proportion of "small" strokes and transient ischemic attacks, reduction of the infarction size, extension of the therapeutic window, and allows the prevention of further brain reperfusion injury. Neuroprotection is conventionally divided into primary, aimed at the interruption of fast mechanisms of necrotic brain cell death, and secondary neuroprotection that provides interruption of the delayed cell death mechanisms (the so-called remote effects of ischemia).

The drug group for the secondary neuroprotection includes antioxidants, anti-inflammatory and trophic factors. However, administration of neuropeptide regulators is the most promising direction of treatment (Semax ®, Cerebrolysin ®). The physiological activity of neuropeptides is greater than the similar effect of non-peptide compounds. While changing the expression of signaling molecules, neuropeptides have a range of various protective effects; they demonstrate significant anti-inflammatory, antiapoptotic, and neurotrophic properties. Given the fact that neuropeptides can easily penetrate the hematoencephalic barrier (in contrast to the polypeptide growth factors), it is difficult to overestimate their potential therapeutic significance.

In recent years, a native neuropeptide protector - Cortexin ®- has been successfully used during ischemic stroke treatment.

-What is so special about Cortexin? What is the mode of action of the drug?

- Cortexin ® is a peptide drug, designed by a team of scientists of the Military Medical Academy under supervision of an academician of RAMS, F.I. Komarov. The drug contains a set of amino acids and polypeptides and a balanced vitamin and mineral composition from the cerebral cortex of pigs, and it has a tissue-specific effect. The mechanism of Cortexin ® action is associated with its metabolic activity: it regulates the ratio of inhibitory and excitatory amino acids, the level of serotonin and dopamine, has GABAergic effects, has an antioxidant activity and the ability to restore the bioelectrical activity of the brain.

It was shown that this drug improves the processes of learning and memory, and stimulates reparative processes in the brain.

Have you confirmed the efficacy of the drug by clinical studies?

- In some pilot studies the efficacy of Cortexin ® in acute ischemic and hemorrhagic stroke has been shown. On the 5th day of treatment the patients receiving the drug demonstrated a rapid regression of neurological symptoms, a more rapid recovery of motor functions, and improvement of functional activity of the brain according to EEG findings and cognitive parameters. However, the results of pilot studies required confirmation in a multicenter randomized double-blind, placebo-controlled study. Such a study of Cortexin ® safety and efficacy in the first acute ischemic stroke was conducted in three hospital centers (Moscow, St. Petersburg and Ekaterinburg). It included the patients admitted to the clinic during the first 12 hours after the onset of their stroke, and they, as you know, are the most difficult patients. Secondary to the uniformed baseline therapy corresponding to the international and national standards, the patients of the first group received Cortexin ® in the dose of 20 mg per day, intramuscularly for 10 days and the second group of patients received a placebo. During the Cortexin ® therapy no side effects and adverse events were reported. Already on day 3-7 of the treatment in the patients of the Cortexin ® group it was possible to observe early recovery of the affected neurological functions and less increase in the size of infarction. By day 28 after the onset of stroke the mortality rate in the Cortexin ® group was 3,1%, while in the placebo group it was 10%. The efficacy of the drug depended on the time of initiation of the therapy: the earlier treatment starts, the more pronounced a positive result is. All these facts create conditions for the use of Cortexin ® in the first hours after stroke in ambulances and in the neuroreanimation units. However it is necessary to conduct well-planned large-scale clinical studies to confirm efficacy and

determine all the features of the action of Cortexin ®

Interviewed by Julia Kuligina