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Stroke, Seasonality, Extension of the Therapeutic Window, Management of Cerebral Edema in Massive Stroke

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ABSTRACT
The article discusses stroke, weather sensitivity, the significance of cold stress, new treatment methods, the possibility of extending the therapeutic window, and the management of cerebral edema in extensive infarction.

Keywords: stroke, seasonality, thrombolysis, therapeutic window, cerebral edema, cerebrospinal fluid

I. INTRODUCTION

Stroke remains one of the most acute and topical medical and biological problems, it ranks second in mortality after coronary heart disease among all nosologies. There is a very high degree of disability and a decrease in the standard of living of people who have had a stroke. Society suffers a huge economic loss. Studies have shown that over the past 30 years, the number of strokes has increased by 70%, and the number of deaths has doubled, in addition, stroke has become much younger " - the incidence rate of young people has increased [1, 2].

Due to the high degree of mortality and disability from stroke, the urgency of the problem, there remains an urgent need to develop new effective methods for diagnosing, preventing, treating and rehabilitation stroke patients.

The **Aim** of this article is to examine the role and significance of the cold factor in the seasonality of stroke incidence, propose new methods for treating stroke, extend the therapeutic window, improving the effectiveness of treatment for cerebral edema.

Materials and Methods: Discussion of the role of seasonal factors—specifically cold—in the development of stroke and an assessment of their significance, a review of existing stroke treatment methods, an analysis of their advantages and disadvantages, proposals for new treatment approaches of stroke, ways to extend the therapeutic window.

II. Seasonality of stroke incidence

There is a clear seasonality and fluctuation in the incidence of stroke and mortality depending on the time of year [3].

In cold seasons, in winter, the incidence and mortality from stroke increases significantly. In the region of Kakheti, Georgia, and in particular in the Telavi Regional Hospital, there is also a clear increase in the incidence

and mortality from stroke during the cold seasons. Scientists from different countries are studying the pathogenic factors that cause this phenomenon.

Among the seasonal pathogenic factors leading to an increase in morbidity and mortality, cold is especially distinguished. Lowering the temperature even by a few degrees leads to a significant increase in the risk of developing acute cerebrovascular diseases. In addition, a seasonal increase in the level of arterial pressure [4] and such complications of arterial hypertension as the same stroke, as well as myocardial infarction [5] in the cold seasons, are known. It is also well known that the seasonal increase in the incidence of respiratory diseases and mortality from them is associated with a decrease in temperature [6].

Summary:

If the wintertime rise in blood pressure and the incidence of stroke and myocardial infarction are linked to cold-induced vasoconstriction, then the use of vasodilators—specifically those targeting cerebral and cardiac vessels—along with increasing the dosage of antihypertensive medications during cold spells, might reduce the spike in stroke and myocardial infarction rates among patients at high risk for these conditions.

To note the special significance of cold as a pathogenic factor in increasing the incidence of seasonal diseases and mortality from them, we propose to call it **„ seasonal cold stress "**.

III. Extension of the therapeutic window

Stroke treatment—basic therapy—until recently relied, and still relies primarily, on infusions, which may be supplemented with antioxidants, neuroprotectors, and antihypoxants. Additionally, anticoagulants and antiplatelet agents are used for ischemic stroke, and hemostatic agents for hemorrhagic stroke.

However, recently there has been a major breakthrough in the treatment of ischemic stroke with the introduction of thrombolysis and thrombectomy to restore perfusion. When these new methods are used during the **'therapeutic window'**—the critical period following a stroke (4.5 hours for thrombolysis [7] and 6 hours for thrombectomy [8] in cases of large artery occlusion) — complete restoration of brain function and the elimination of neurological deficits are possible. If the therapeutic window is incorrectly assessed and the above-mentioned treatments—thrombolysis or thrombectomy — are implemented too late, after the therapeutic window has passed, the treatment will be ineffective and serious complications, including cerebral hemorrhage, are possible.

Recent studies allow thrombolysis to be performed if MRI/CT perfusion data reveal a small infarct core and a large penumbra, within 9 hours after stroke when using alteplase [9] and within 24 hours when using tenecteplase [10]. The therapeutic window for thrombolysis has also been extended to 24 hours [11].

According to large clinical studies, for every minute of delay in thrombolysis, the brain loses 1.9 million neurons. Therefore, the "golden hour" rule has been adopted: the in-hospital time from the moment a patient is admitted to the hospital until the start of thrombolysis should not exceed 60 minutes[12].

To reduce the time from stroke diagnosis to the start of thrombolysis, some countries—the United States, Germany, and Australia—have already used ambulances[13] equipped with CT scanners, mini-laboratories for rapid testing, thrombolysis equipment, and videoconferencing with a neurologist at the hospital. Thrombolysis begins in the ambulance.

Despite the fact that the latest technologies make it possible to extend the “therapeutic window” to 9–24 hours, thrombolysis continues to be administered in the first 3–4.5 hours, since in most cases primary stroke centers do not have the ability to provide MRI/CT perfusion. Thrombectomy is still primarily performed within the first six hours after stroke diagnosis. Therefore, if the primary and secondary stroke centers are located significantly apart, transporting the patient from the primary center to the secondary stroke center within the first six hours — the "therapeutic window" — is, in most cases, impossible.

At Telavi State University and the Telavi Regional Hospital, we have developed a device for cerebrospinal fluid (CSF) oxygenation (Fig.1) that also enables the administration of medications into the CSF and the lowering of cerebrospinal fluid temperature, thereby reducing hypoxia and cerebral edema.

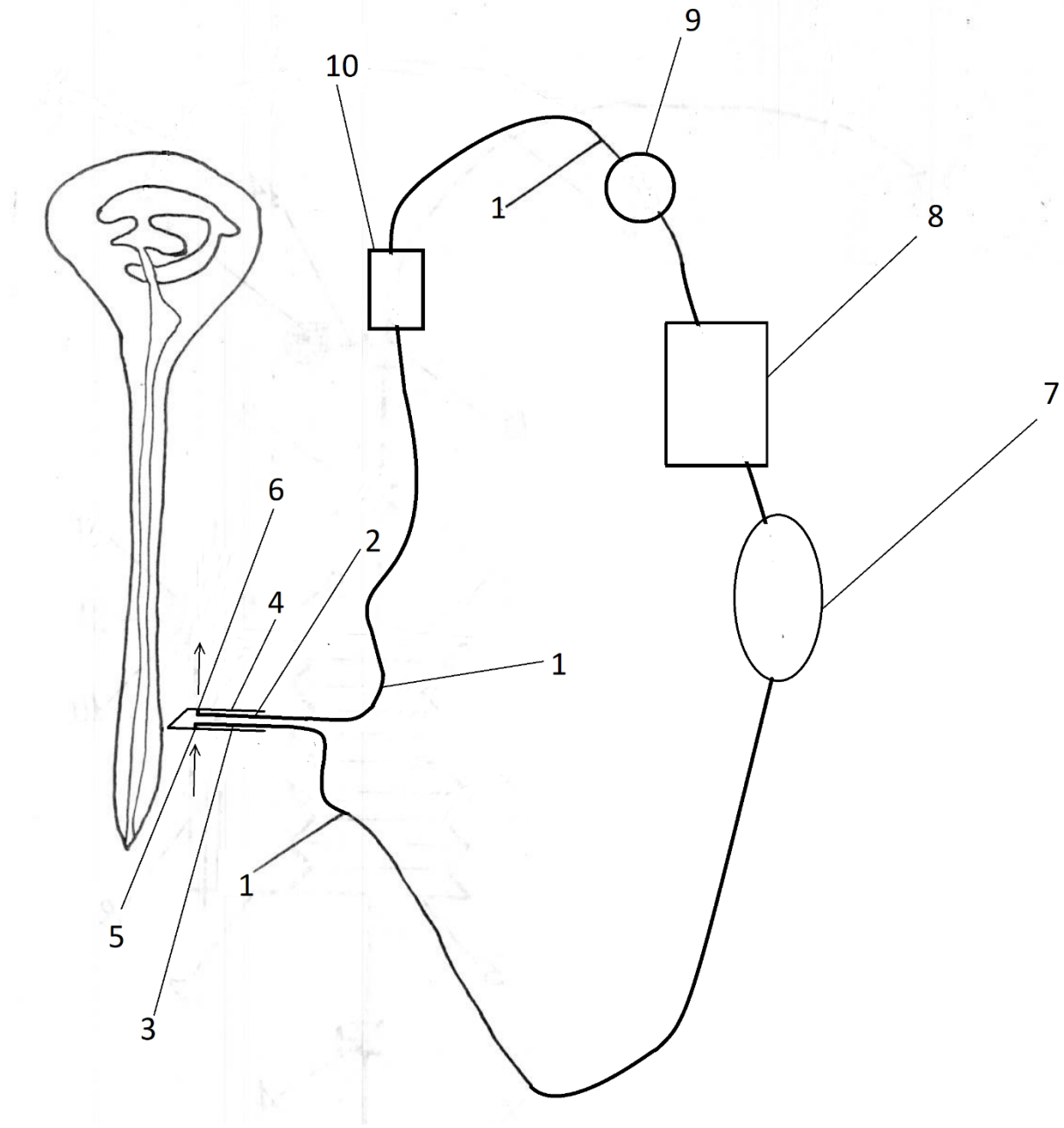


Fig.1

Device for cerebrospinal fluid oxygenation

1 – flexible tube, 2, 3 – channels of the dual-channel catheter, 4 – dual-channel catheter, 5, 6 – openings of the dual-channel catheter, 7 – drug administration reservoir, 8 – pump, 9 – oxygenator, 10 – heat exchanger

The device for cerebrospinal fluid oxygenation comprises a flexible tube 1, the ends of which are connected to channels 2 and 3 of a dual-channel catheter 4; one end of tube 1 is connected to one channel 2 of catheter 4, and the other end of the tube is connected to the other channel 3 of catheter 4. The channels open at the other end of the catheter (opposite the connection point of the flexible tubes) via openings 5 and 6 located on opposite sides of

the catheter. The flexible tube 1 is connected to a reservoir 7 for drug administration (such as an Ommaya reservoir, though located outside the patient's body), a pump 8, an oxygenator 9, and a heat exchanger 10 (cooler).

Catheter 4 is inserted into the spinal subarachnoid space via lumbar puncture. Pump 8 is then activated; cerebrospinal fluid is withdrawn from the spinal canal through opening 5 of catheter 4 and reintroduced into the spinal canal through opening 6 of catheter 4 (the directions of fluid inflow and outflow are indicated by arrows). Oxygenator 9 makes it possible to increase the oxygen content of the cerebrospinal fluid and improve oxygen supply to neurons, while heat exchanger/cooler 10 allows for lowering the temperature of the cerebrospinal fluid and the brain, thereby reducing nerve cell activity and oxygen demand. Reservoir 7 enables the administration of neuroprotective agents into the cerebrospinal fluid.

IV. Results:

This device can be used if, following a stroke, the time of therapeutic window for thrombolysis has already closed but there is still time to perform a thrombectomy.

If there is still time to administer thrombolytic therapy, this device is not used, as a lumbar puncture performed within the preceding 7 days is considered a relative contraindication, and one performed within the preceding 24 hours is an absolute contraindication to such therapy. This precaution is intended to prevent the development of a spinal hematoma and subsequent spinal cord compression, which could lead to paraparesis or paraplegia of the limbs.

Specialized stroke ambulance teams can be equipped with this device. Upon the team's arrival, if the time window for thrombolysis has expired or is running out, the device's catheter is inserted into the lumbar space, and an intrathecal infusion begins. This process boosts oxygen supply to the brain, administers neuroprotective agents, and induces cerebral hypothermia to reduce the oxygen demand of brain cells. This approach helps salvage a significant portion of the ischemic penumbra and minimize brain cell death (an estimated 1.9 million neurons die every minute during an untreated stroke) prior to thrombectomy; furthermore, it extends the therapeutic window for performing the thrombectomy procedure.

If a specialized stroke team equipped with a CT scanner diagnoses a hemorrhagic stroke, this device can be put into use immediately.

V. Cerebral Edema in Stroke: Treatment

Cerebral edema is a serious complication of stroke. It develops in approximately one-third of stroke patients and is among the most dangerous — and often fatal — complications. Stroke-induced edema primarily develops via vasogenic and cytotoxic mechanisms; however, in cases involving hemorrhage or focal edema near cerebrospinal fluid pathways—leading to their compression — a hydrocephalic mechanism may also be involved [14–16].

Intracranial hypertension syndrome and the pathophysiology of cerebral edema are best understood within the framework of the Monro-Kellie doctrine [17, 18], formulated in the late 18th and early 19th centuries. According to this theory, the cranium constitutes a rigid, fixed-volume container holding three components in a state of strict balance: brain tissue (~85%), blood (~8%), and cerebrospinal fluid (CSF) (~7%). The development of a tumor, hygroma, or hematoma within the brain introduces an additional pathological volume. The sum of the intracranial component volumes remains constant: $V_{brain} + V_{blood} + V_{CSF} + V_{pathological_object} = Constant$.

Under normal conditions, their interaction maintains a stable pressure within the range of 7–15 mm Hg.

As cerebral edema progresses or the additional pathological volume increases—once compensatory mechanisms (displacement of cerebrospinal fluid into the spinal canal and venous blood into the sinuses) are exhausted (i.e., when the brain, having expanded due to edema, fully occupies the reserve/compensatory space — the sum of the CSF and venous blood volumes capable of being displaced into the spinal canal and sinuses)— even a slight increase in volume triggers a sharp spike in intracranial pressure (ICP). This leads to compression of cerebral blood vessels and, consequently, reduced CSF outflow and decreased cerebral perfusion pressure (and thus perfusion); this, in turn, leads to cerebral ischemia and creates a vicious cycle:

1. Cerebral edema leads to an increase in intracranial pressure.
2. High pressure causes compression of capillaries and veins, which impairs blood flow to the brain.
3. Oxygen deprivation (ischemia) triggers cerebral edema.

4. The edema further increases tissue volume, leading to a critical rise in intracranial pressure.

As the ischemic process progresses, gradual death of brain tissue occurs.

Furthermore, severe complications of cerebral edema include brain shift syndromes, the most dangerous of which is brainstem herniation. These are critical, life-threatening conditions that require treatment in an intensive care unit.

Management of intracranial hypertension [19, 20] in light of the Monro-Kellie doctrine is achieved in two ways: 1. Reducing the volume of the cranial contents; 2. Increasing reserve space.

Reducing the volume of the cranial contents aims to remove an additional—pathological volume such as a hematoma in the case of a hemorrhagic stroke, a tumor, etc. or to decrease the volume of one or more intracranial components, with the goal of lowering intracranial pressure to below 20 mm Hg. To achieve this, the following measures (actions) may be employed:

Reduction of parenchymal volume and edema (brainV) is achieved through osmotherapy —the administration of hypertonic solutions (such as mannitol or hypertonic NaCl). These create an osmotic gradient, "drawing" water from the brain tissue into the bloodstream. Glucocorticoids are also used; they are primarily effective against vasogenic edema (associated with tumors) because they restore blood-brain barrier permeability.

To reduce blood volume (blood V), hyperventilation is employed: patients are administered high doses of oxygen via mechanical ventilation to ensure that the remaining brain cells receive adequate nourishment. Lowering blood CO2 levels causes constriction of the cerebral arterioles (vasoconstriction), thereby reducing intracranial blood volume. The head of the bed is elevated by 30° to improve venous drainage.

Hypothermia and pharmacological sedation are used to reduce the metabolism of nerve cells, thereby decreasing their demand for blood and oxygen and, consequently, cerebral ischemia [21, 22].

Reduction of cerebrospinal fluid volume (CSF V): To achieve this, external ventricular drainage is performed — placing a catheter into the brain's ventricles to drain excess cerebrospinal fluid.

Increasing reserve space—decompressive craniectomy: surgical removal of a portion of the cranial vault bones [22, 23]. This actually "negates" the Monro-Kellie doctrine, transforming a closed system into an open one and providing the brain with room to expand without a critical rise in pressure.

To treat cerebral edema — including cases associated with stroke — we developed a "Device for regulating cerebrospinal fluid pressure and circulation" at the Tbilisi State Medical Institute; this device was subsequently refined at Telavi State University and the Telavi Regional Hospital [24].

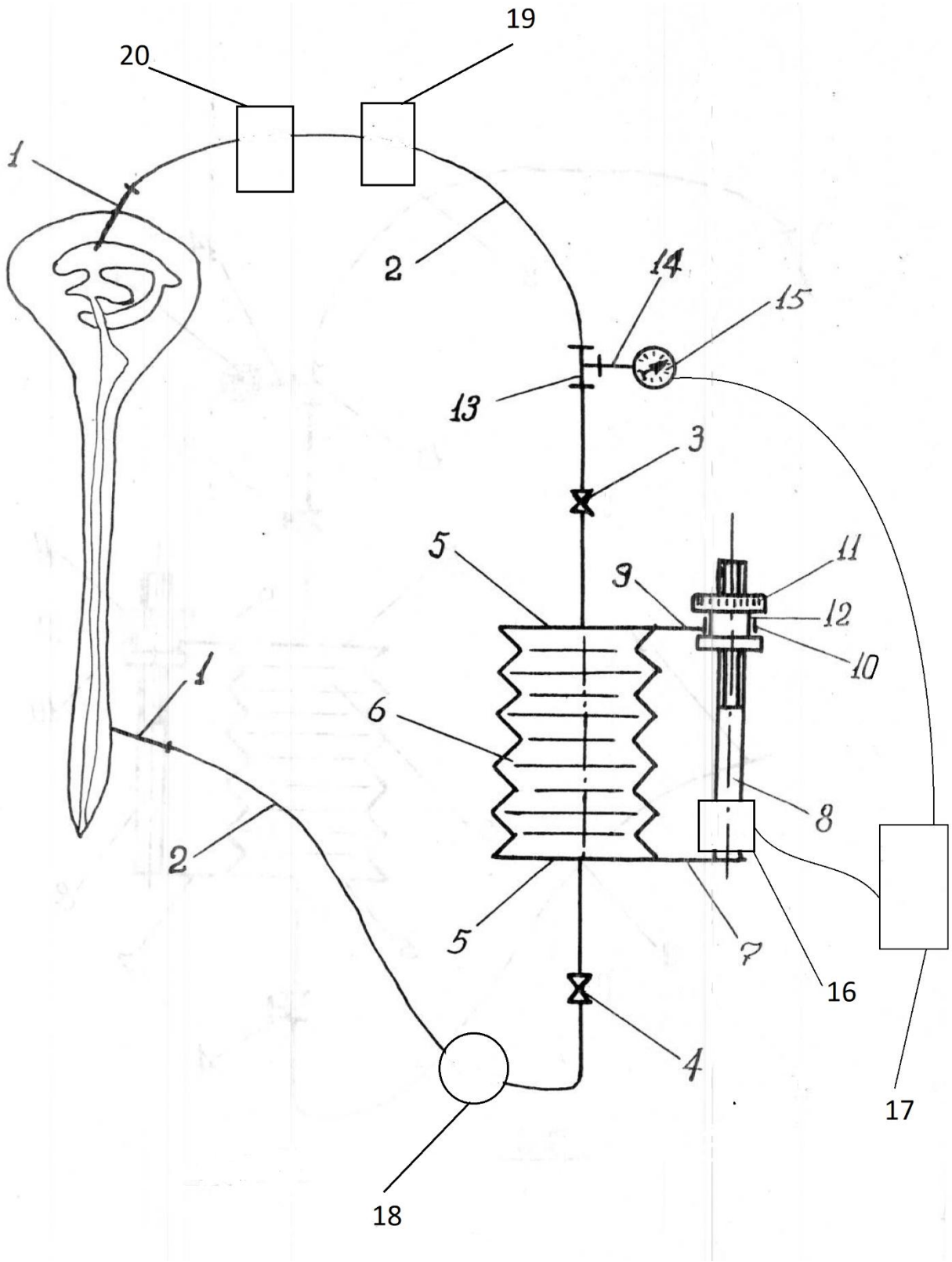


Fig.2 The device for regulating cerebrospinal fluid pressure and circulation

The device for regulating cerebrospinal fluid pressure and circulation consists of a corrugated cylinder 6, the ends 5 of which are connected to a screw mechanism 8, 11 that allows its volume to be adjusted. The ends 5 of the corrugated cylinder are connected to tubes 2, the ends of which are attached to needles or catheters 1; one of

these is inserted into the lumbar space, and the other into a brain ventricle. Stopcocks 3 and 4 are installed on the tubes.

VI. RESULTS

The device restores cerebrospinal fluid (CSF) circulation when the CSF outflow pathways are compressed, and allows for the regulation of CSF pressure by adjusting the volume of the corrugated cylinder (6) via a screw mechanism. To increase CSF pressure, the volume of the corrugated cylinder is reduced while stopcock 3 on tube 2 — the end of which is inserted into the brain ventricle — is closed, and fluid (CSF) is introduced into the lumbar space. If it is necessary to lower cerebrospinal fluid (CSF) pressure by increasing the volume of the corrugated cylinder, stopcock 4 on tube 2 — the end of which is inserted into the lumbar space — is closed, and CSF is drained from the brain ventricle. This selective closing of valves during the regulation of CSF pressure prevents the herniation of brainstem structures. Valves can be installed in place of stopcocks to perform the same function. This device allows for an expansion of the reserve volume, creating an externally adjustable reserve space. In the presence of an obstruction to the outflow of cerebrospinal fluid (CSF), this device creates an alternative pathway for its circulation, which also helps to reduce brain edema and lower intracranial pressure. The screw mechanism can be connected to a pressure gauge (15), a micro-electric motor (16), and a computer (17), enabling the automatic regulation of intracranial pressure.

Medications to reduce brain edema—for example, neuroprotectants or steroids — can be introduced into the corrugated cylinder 6.

Furthermore, the device can be connected to a pump 18, a cooler 19, and an oxygenator 20; the pump serves to accelerate cerebrospinal fluid circulation, the oxygenator increases the oxygen content in the cerebrospinal fluid, and the cooler enables the induction of cerebral hypothermia.

All of this—intrathecal infusion of medications, as well as oxygenation and hypothermia of the cerebrospinal fluid and the brain—helps to reduce brain edema.

If the device is connected to a column containing a sorbent, cerebrospinal fluid (CSF) sorbent treatment can be performed.

In addition, the device facilitates the collection of cerebrospinal fluid for analysis and monitoring.

Thus, the proposed device — The device for regulating the pressure and circulation of cerebrospinal fluid — makes it possible to reduce intracranial hypertension by employing the both approaches: decreasing the volume of the cranial contents and increasing the reserve space. Furthermore, it enables the restoration of cerebrospinal fluid circulation in the event of an obstruction within the cerebrospinal fluid pathways.

The use of this device in cases of severe brain edema may obviate the need for a craniectomy to increase reserve space and decompress the brain.

VII. CONCLUSION

Given the significance of the issue, research into stroke continues to be pursued intensively across all areas.

In our view, modern medicine does not pay sufficient attention to the study of seasonal pathogenic factors, which play a significant role in the fluctuations of morbidity and mortality rates associated with seasonal diseases. It is worth recalling the experience of ancient Chinese medicine, which paid close attention to these factors, identified a number of them, and studied their pathogenic effects. We believe that more intensive study of these factors and their pathogenetic impact would make it possible to at least mitigate the seasonal rise in morbidity and mortality from these diseases.

The Monro-Kellie doctrine is widely used to analyze the pathogenesis and guide the choice of treatment strategy for cerebral edema and increased intracranial pressure in each individual case.

We propose that volumes connected to the cerebrospinal fluid system for curative purposes —such as an Ommaya reservoir or the "Device for regulating the pressure and circulation of cerebrospinal fluid" (containing a corrugated cylinder) that we have proposed — be termed a "Curative volume." Furthermore, formations that arise in the brain as a result of a pathological process — such as a hematoma, a tumor, etc. — should be referred to as a "pathological volume" rather than an "additional volume."

The proposed device for cerebrospinal fluid oxygenation in acute ischemic stroke can be used when thrombolysis is not performed, as damage to the vessels of the internal vertebral plexuses — particularly the epidural venous plexuses — could lead to the development of a spinal hematoma and spinal cord compression.

It is conceivable that advancements in spinal puncture technology — aimed at reducing the risk of hemorrhagic complications and improving hemostatic techniques — will make it possible to use the developed device immediately prior to thrombolysis.

Coating the catheter with bio-glue prior to its insertion into the lumbar space — before thrombolysis — might stabilize the walls of damaged vessels during insertion and prevent bleeding both during and after the thrombolysis procedure.

It should be noted that in a number of cases where thrombolysis was no longer feasible —because the therapeutic window had already closed — our use of a combination of cardiomagnyl, clopidogrel, and enoxaparin, together with dipyridamole, resulted in the complete resolution of neurological deficits. In this combination, when replacing enoxaparin with warfarin, we obtained the same results

Research has led to the development of artificial blood — an oxygen carrier used when donor blood is unavailable. There have been attempts to use intrathecal infusion of artificial blood to improve oxygen supply to the brain during a stroke [25]; however, due to serious complications, this method has not been successfully implemented. An artificial cerebrospinal fluid has also been developed [26], which is used for irrigating the subarachnoid space, restoring volume during surgical procedures, and in experimental neurobiology.

Research should likely be intensified into the development of an artificial oxygen carrier suitable for intrathecal administration without causing complications, as well as into the creation of an artificial cerebrospinal fluid that additionally functions as an oxygen carrier.

There is an increasing number of publications concerning intrathecal perfusion; meanwhile, intrathecal baclofen therapy — which has been in use for several decades — has seen significant advancement [27] in the treatment of spasticity in both children and adults.

There is no doubt that intrathecal perfusion will play a significant role in the future management of serious brain disorders, particularly within the fields of neuro-intensive care and psychiatric intensive care.

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