Vicious circles in the pathogenesis of schizophrenia (new principles of pathogenesis and treatment of schizophrenia)

Voronov Alexandr Ivanovich

Candidate of Medical Sciences. The doctor is a psychiatrist.

Clinic for pathology of higher nervous activity

Abstract. Long-term observations of patients who underwent cytokine therapy in our clinic allowed us to create a fundamentally new concept of the pathogenesis of schizophrenia and to find a number of instrumental examinations capable of confirming or rejecting the diagnosis of F 20. We came to the conclusion that neural networks suffer secondarily. The main reason for the onset and development of schizophrenia is the genetic vulnerability of astroglial syncytium. We believe that the greatest success of the use of cytokines is not a long-term stable remission, but a complete recovery of patients F 20, which was confirmed socially, clinically and instrumentally.

Keywords: Cytokines, Astroglial networks, Tripartite synapse, Delta sleep, New concept of schizophrenia pathogenesis, New principles of schizophrenia treatment.

Schizophrenia – ***a disease based on the self-poisoning of the brain, as an organ, by the products of its own metabolism.*** The genetic vulnerability of astroglia reduces the drainage function of the glymphatic system. The growing toxicity of the cerebrospinal fluid leads to the degeneration and death of a number of glial cells, which in turn triggers a chain of pathophysiological processes developing according to the laws of a “vicious circle”. Neurons are deprived of the energy support of astrocytes. Tripartite synapses change sensitivity to most neurotransmitters (GABA, dopamine, serotonin, etc.), and they change in different directions. In the toxic cerebrospinal fluid, oligodendrocytes die en masse, depriving axons of myelin isolation. Decreased energy potential, distortion of emotional space, impaired attention and thinking, delirium, pseudo-hallucinations are just various **consequences** of this progressive autointoxication process. "**Consequences**" are depicted in the form of shadows from the pathophysiological processes going on in the central nervous system of patients F 20 (Fig. 2).

Agree, our idea of F 20 is fundamentally different from everything that you have ever read about this disease [7.]. For practicing psychiatrists, the definition is not familiar, but it reveals the pathophysiological mechanism of the development of schizophrenia correctly. Pathologist-psychiatrist Pavel Evgenievich Snesarev, in the fifties of the last century, gave a

shorter definition of schizophrenia: **"Toxic - anoxic encephalopathy"** [1.] Eighty years ago, his instrument was only a microscope, hellish patience and the most complex methods of staining the gliosis tissue of the brain he himself developed... Who knows, if it were not for the young AV Snezhnevsky, who for political reasons took his place - what heights could Soviet psychiatry have reached? The scientific views of Pavel Evgenievich were formed by the school of V.M.Bekhterev, where the experiment and the close connection of pathomorphology with clinical observations were always the basis. Unfortunately, Snezhnevsky, for all his merits, took Soviet psychiatry in a completely different direction and doomed it to the role of a "servant" of the political regime.

If we consider pathogenesis as an alternating sequence of events, then the first event that triggers the schizophrenic process, we assume a shift in the cytokine balance towards the prevalence of the group of cytokines **Th2>Th1**. This is followed by an autoimmune attack of cytokines of the **Th2** group on the "legs" of astrocytes lining the perivascular space. The consequence of this attack is a violation of the coordinated coordination of the changing volume of the "legs". The mechanism that provides enhanced movement of the cerebrospinal fluid along the glymphatic system breaks down during slow wave sleep [2,10.]. An autoimmune attack on the "legs" of astrocytes becomes the cause of the launch of the main vicious circle in the pathogenesis of schizophrenia, But! Just an incentive. Schizophrenia should not be classified as an autoimmune disease, despite the severe immunological imbalances observed in patients. The main pathological mechanism that determines the entire course of schizophrenia is the genetic vulnerability of astroglial syncytium, which actually organizes the drainage of the cerebrospinal fluid through the glymphatic system in slow sleep. We have written a lot about this in previous articles [2,3,5,9,10.]. Moreover, due to the breakdown of this drainage mechanism, it is impossible to compensate for slow-wave sleep after its deprivation. Patient F 20 is unable to “sleep off” after a sleepless night. Even a small "lack of sleep" is destructive for him. This is a serious provoking factor capable of independently launching the main vicious circle, accelerating the degradation of astroglia. (Fig. 1, blue circle in the center.) It happens in the following way; A shift in the cytokine balance **Th2> Th1** adversely affects the domain-coordinated, sequential change in the volume of astrocyte legs [2,10]. Astroglial syncytium ceases to provide increased flow of cerebrospinal fluid during slow sleep and metabolic products accumulate in the cerebrospinal fluid. Astrocytes in both directions pass through all the toxins that the stagnant cerebrospinal fluid contains and gradually degrade. Within three to five years, this process leads to the appearance of defective symptoms. Defective symptomatology, as a rule, appears before psycho-production, and sometimes even grows without psycho-production (simple form F20) Astrocytes suffering in toxic cerebrospinal fluid are not able to energetically support neurons.

The energy potential is steadily declining. Astrocytes cease to adequately provide sensitivity to mediators in trypartite synapses. In different parts of the brain, the sensitivity to neurotransmitters changes in different directions, but basically it increases to dopamine and decreases to serotonin.

Our understanding of the pathogenesis of schizophrenia (Fig. 1.2.)

The central nervous system (CNS) is made up of individual cells, but the brain functions harmoniously as a single organ. Almost all the cells present in the brain matter conditionally divide into two large interdependent network structures that are organized in different ways; 1. **Neural** networks are united by the electric action potential and neurotransmitters moving in the space of the synaptic cleft. Neurons hardly reproduce. In the growing autointoxication of the cerebrospinal fluid, they suffer, but almost never die. Therefore, **the intellect of the patient F 20 remains intact**, even in conditions of attention deficit, distortion of emotional space and a significant drop in energy potential. ***This feature allows patients to consider themselves mentally healthy, and to assert this, ignoring the other opinion of relatives and doctors.***

2.**Astroglial networks** are organized differently, according to the syncytium principle, where there is no electrical action potential, and individual cells proliferate intensively. Astrocytes constantly multiply, renew themselves, combine into domains and communicate with each other with molecules completely different from neurotransmitters. The increasing inconsistency of fluctuations in the volume of astrocytic "legs", which tightly surround the entire perivascular space, reduces the velocity of the cerebrospinal fluid in the glymphatic system of the central nervous system. It is now well known that only in slow sleep occurs the most intensive disposal of the brain, as an organ, from the products of its own metabolism. Until the invented psychotropic drug capable of restoring the physiological structure of night sleep. All types of schizophrenia, including some types of autism, share a lack of drainage function of slow wave sleep, although to varying degrees.

All therapeutic efforts of psychiatrists and pharmacologists are aimed at correcting the action of neurotransmitters in interneuronal synapses. (Fig. 1. Yellow circle on the right) In this case, the pathology of astroglial syncytium, the main reason for the increasing deficit of slow wave sleep, is ignored (Fig. 1. Central blue circle). For psychotropic drugs, there is no point of application. We argue that the main reason for the development of schizophrenia lies precisely in the pathology of astroglial syncytium. Any failure in its well-coordinated work upsets many of the brain functions closely related to it. Increasing, according to the principle of a vicious circle, intoxication of the cerebrospinal fluid modifies astrocytes, inhibits their proliferation. Usually, the pathological process in astroglial networks is slow. Intoxication with the products of one's own metabolism builds up gradually, over the course of three to five years, and only then leads

to a tangible defect. But there is also an avalanche-like increase in the process (toxic, hyperthermic schizophrenia). In any case and always, the development of schizophrenia is based on a decrease in the draining function of delta sleep, the only organizer of which is astroglia. Astrocytes are reborn and gradually **lose the ability to energetically support neurons,** cease to adequately **regulate trypartite synapses**. The process leads to a drop in the energy potential, a change in the sensitivity of interneuronal trypartite synapses to dopamine, serotonin, gamma aminobutyric acid (GABA) and other mediators.

The increasing toxicity of the cerebrospinal fluid triggers at least two more vicious circles. **The second vicious circle** (Fig. 1. Yellow on the right) was defined and became clear only after the discovery of tripartite synapses. Astrocytes, which have changed their properties in the toxic cerebrospinal fluid, in different parts of the brain, modulate the work of trypartite synapses in different directions. As a result, the usual concentration of dopamine, serotonin and other mediators in certain areas of the brain works as excessive, and in other areas, as insufficient. All modern psychopharmacology is engaged in correcting the sensitivity of these synapses, with varying success. Antipsychotics, by their presence, balance the activity of neurotransmitters in interneuronal synapses, without affecting astrocytes in any way - the main reason that disrupts the balance of mediators. The selection of antipsychotics, antidepressants and other psychotropic drugs in practice occurs according to the **ex juvantibus** principle (if it helps means it is prescribed correctly) and depends entirely on the clinical experience of the doctor.

The third vicious circle (Fig. 1, red circle left), - is triggered by the growing intoxication of the cerebrospinal fluid and begins with the mass death of oligodendrocytes. The lack of myelin manifests itself in a slowdown in the speed of the impulse through Ranvier's interceptions. The myelin of axons is thinning (up to the complete absence in some areas). This leads to a dispersion of the impulse, the so-called "worn out wires symptom" and causes many clinical symptoms interpreted as pathology of thinking (Fig. 2, left shadow). It is with these symptoms that psychiatrists try to substantiate the diagnosis. Each doctor in a conversation with a patient evaluates the "found" symptoms subjectively - hence the confusion in the interpretation of "findings" and disputes about the diagnosis up to the denial of the very presence of schizophrenia, as a disease with a single pathogenesis, but very different symptoms.

In our studies, we used three objective diagnostic techniques that allow us not only to substantiate or reject the diagnosis of schizophrenia, but also quantitatively, digitally and on a graph (instrumentally) to observe the dynamics of the recovery of our patients. We recommend these methods for early and objective diagnosis of schizophrenia.

1.Pre-pulse inhibition. (PPI). This method is used to confirm the diagnosis of schizophrenia in laboratory rats and mice. The presence of the "mouse model of schizophrenia" has made it possible to defend more than one doctoral dissertation. In fact, this test measures the amount of "attention" and expresses it in numbers. Physiologically, attention is provided by sufficient myelination of axons, a normal rate of potential conduction through Ranvier's interceptions, which indicates a good state of oligodendrocytes, the only sources of myelin. If oligodendrocytes suffer, myelin becomes low. Isolation of axons is disturbed - the impulse is not channeled, but scattered, then it is difficult to keep attention. The diagnosis of schizophrenia is always accompanied by degeneration and death of oligodendrocytes. Thinning of the myelin sheath of axons, up to the complete absence of myelin in certain areas, makes it impossible to maintain attention. In our case, the insulating sufficiency of myelin on the axons of the auditory areas of the brain is being investigated. Anatomically, the auditory (temporal) zones are drained by the cerebrospinal fluid more difficult than other zones, therefore, the death of oligodendrocytes in the temporal regions occurs earlier than in the occipital, visual zones. But on the axons of the visual zones, it is also possible to determine the sufficiency of myelin, for example, by the nature of eye movement.

The **PPI** procedure on a person looks like this; the subject is comfortably seated in a comfortable armchair in a room well insulated from extraneous sounds. The eyes are closed. In high-quality headphones, a special device generates "white noise" (reminiscent of the noise of rain). Sensors are fixed under the eye and on the forehead that register the subject's reaction to clicks heard in the headphones. The clicks are loud, and anyone who hears such a click against the background of "white noise" involuntarily shudders and blinks. The flinch is registered by the sensors. It is impossible to forge a test. It has been experimentally proven that a mentally healthy subject, if 60 milliseconds before the main loud click, give a barely audible, quieter pre-click, does not flinch. A subject with a lack of attention ignores the pre-click and always flinches at the next loud noise. Lack of attention is often recorded in blood relatives of the patient, although to varying degrees. Expressed in numbers - attention deficit allows with a high probability to assume from which parent the patient inherited a predisposition to schizophrenia. In our experiment, immediately after inhalation of a mixture of cytokines, the PPI numbers slightly changed towards improving attention. This allowed us to more accurately select the combination of cytokines. In the course of cytokine therapy, the "attention numbers" gradually increase, until they approach the norm. The therapeutic mixture of cytokines has not only a cumulative effect, but also slightly and briefly improves attention immediately after the procedure. We use this feature to correct the ratio of cytokines in the inhaled mixture.

The F 20 diagnosis test is simple and excellent. It can be used to test people whose profession requires high responsibility and absolute mental health (pilots, train drivers, military specialists in rocket launchers, individual leaders and politicians).

In 2012, Scottish scientists at the University of Aberdeen discovered that people with schizophrenia are unable to track moving objects smoothly. The device created by them records the lag of the gaze of patients with F 20 from the object of observation. The diagnostic accuracy is close to 98%. This method does not require sound insulation, a "white noise" generator, sensor stickers, a special cabinet and takes only a few minutes. This is in theory. In practice, there are no such simple and inexpensive devices in Russian hospitals, and given the current state of medicine, one should not expect them to appear...

2. Dynamics polysomnography. Polysomnography has been around for a long time and is mainly used to prevent respiratory arrest during sleep (apnea) and to combat snoring. The realization that this method can be used to accurately diagnose schizophrenia has come recently. Why a person spends a third of his life on sleep - it became clear only a few years ago. **In schizophrenia, there is always a deficit in "slow wave sleep".** This is the main instrumental diagnostic criterion. It cannot be detected without polysomnography. Only and exclusively in slow sleep is the flow of the cerebrospinal fluid through the glymphatic system seriously accelerated. Any decrease in the time or depth of slow wave sleep leads to the accumulation of metabolic products and self-poisoning of the brain as an organ. Autointoxication of the cerebrospinal fluid causes the death of two of the four types of microglial cells involved in the organization of REM sleep. (Fig. 1: red circle on the left) As a result, REM sleep suffers, but this is not as critical as NREM sleep deficit. When getting rid of metabolic products is difficult, toxicosis increases. In a toxic environment, oligodendrocytes die and the morphology of astrocytes changes. The morphology of astrocytes changes according to the laws of a vicious circle. The more intoxication, the more astrocytes change; they lose ribosomes, increase in size. The more the morphology of astrocytes changes, the worse they cope with organizing the movement of the cerebrospinal fluid along the glymphatic system. The proliferation of astrocytes slows down, and the ability to accelerate the movement of cerebrospinal fluid in slow sleep decreases (Fig. 1. The main blue circle in the center). Astrocytes are interconnected in astroglial networks according to the syncytium principle. **It is very likely that these connections are much more complex than neural networks.** There are no mediators on which psychotropic drugs could act, but astrocytes are sensitive to any changes in the ratio of cytokines. Actually, **all our therapy is aimed at restoring the cytokine balance.** We determine the effectiveness of cytokine therapy by the dynamics of restoration of the depth and duration of slow wave sleep. The polysomnography procedure takes place at the institute at night, although it is more

informative to carry out it continuously, for two to three days, like Holter monitoring. Such devices already exist without wires and work perfectly within a radius of 30-50 meters. The quality and quantity of slow wave sleep shows not only the momentary severity of the schizophrenic process, but also the approximate duration and intensity of the disease. We have written a lot about this in previous articles. [2,3,5,6.] Slow sleep should normally be at least 26%. If the percentage is less, this indicates a low drainage function of the glymphatic system and is an important sign of schizophrenia.

3.Three Tesla MRI. We conduct this expert examination at the entrance, before starting cytokine therapy and then every six months. We pay close attention to the dynamics of the Virchow - Robin perivascular spaces. So - the less the depth and duration of the delta sleep - the slower the cerebrospinal fluid flows, the higher its toxicity, the greater the pressure in the glymphatic system! This causes expansion of the ventricles, coarsening of the intraventricular vascular plexuses, the appearance of microhemorrhagic changes on them, an increase in the number and size of Virchow-Robin spaces. Under such conditions, the degeneration of astrocytes is more intense. They lose ribosomes, slow down proliferation, and some increase in size [4]. In the case of a well-chosen combination of cytokines and a rapid restoration of a full night's sleep, the Virchow-Robin spaces decrease and return to normal within a year or two. Sometimes they disappear completely [3,10.]. We are not satisfied with the written conclusions of radiologists and without fail every six months we compare the control parts of the brain (with the enlarged perivascular spaces). So we manage to instrumentally observe the dynamics of restoration of the drainage function of the glymphatic system.

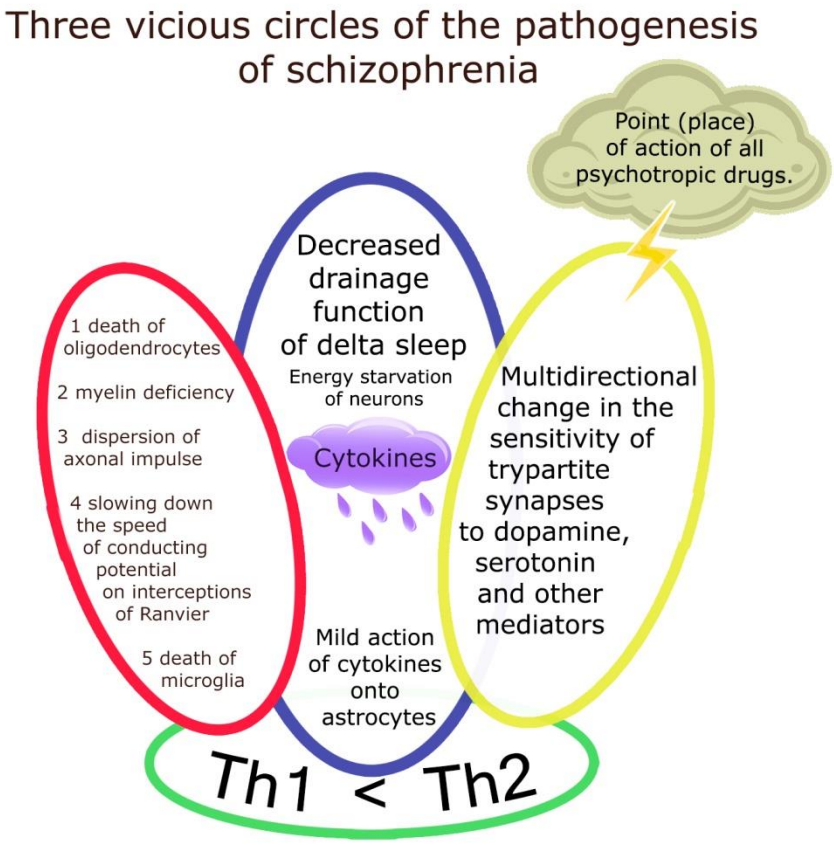
Follow-up of real patients who underwent a course of treatment with cytokines.

1. Patient "L" The disease began in winter 2009. The debut within a month was stopped by drip parenteral administration of cytokines. In the spring of 2010 she entered the medical institute (see the appendix to the patent). In the winter of 2010, during the winter session, she was admitted to the psychiatric hospital №2 of Novosibirsk. Diagnosed with paranoid schizophrenia. In a state of catatonic excitement, in mating, at high doses of haloperidol, she was in the hospital for more than two months without visible improvement. At the request of the parents, treatment with cytokines was started again. The course is three months. She was discharged in a state of stable remission. In the fall of 2011, she entered a medical school and graduated from it with excellent results. Got married. By July 2021, she gave birth to three children, married for the second time. Additionally, he is raising a child of a new husband. Graduated by correspondence from the Novosibirsk University of Railway Engineers. Mentally completely healthy. Follow-up for 11 years. [5.8.]. Monitoring continues.

2. Patient "Carol". She fell ill in 2010 at the age of 14. She was hospitalized in psychiatric hospitals twice in 2011 and 2012. She was treated with haloperidol, clopixol, antidepressants. For ten months she was treated exclusively with cytokines. It is described in great detail in the journal [6.10]. By July 2021, the follow-up is 11 years. She got married, graduated from the Institute of Railway Engineers, and got a prestigious job in Moscow. Mentally completely healthy.

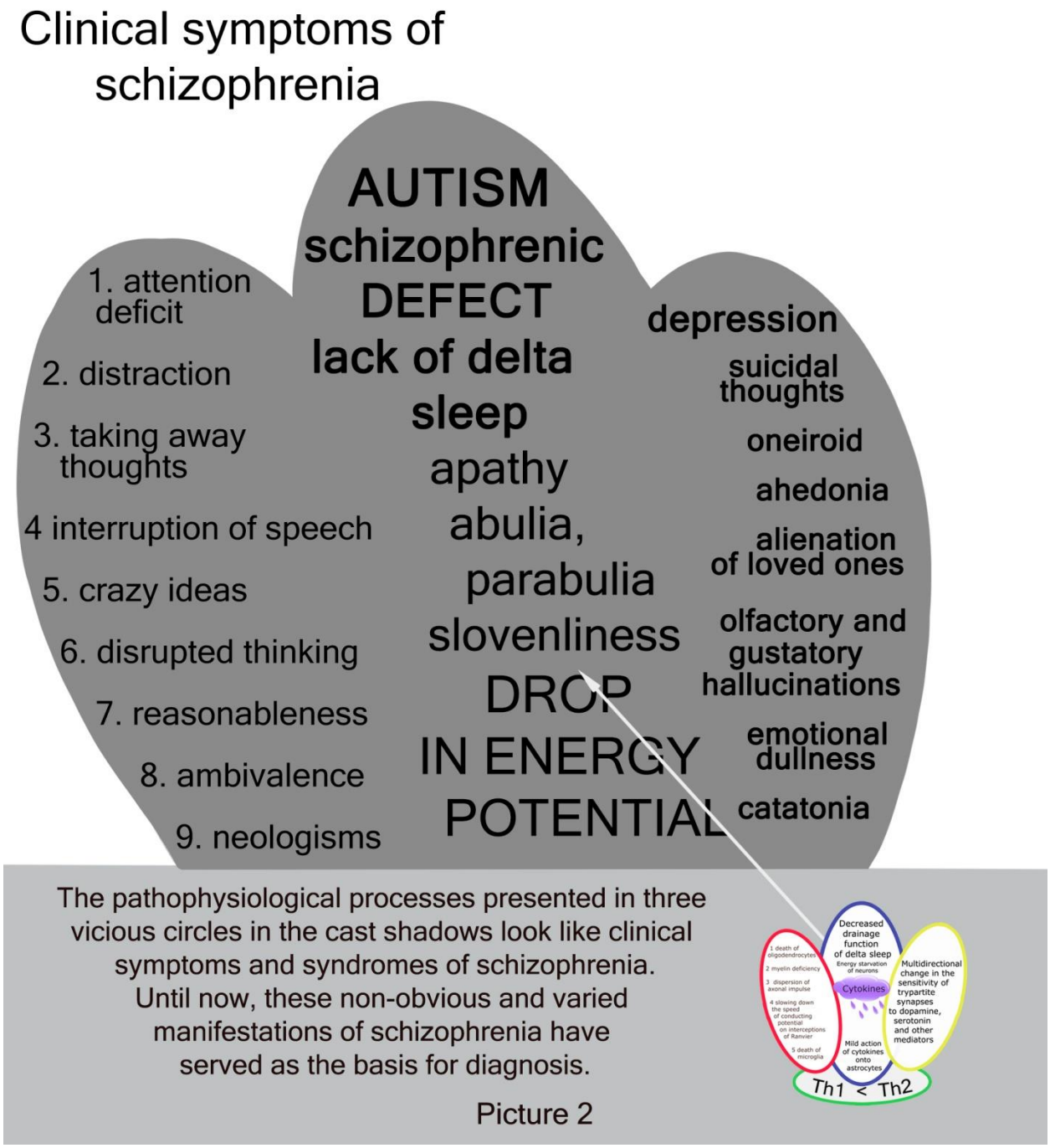
3. Patient "I" is 29 years old. He has been suffering from schizophrenia since 2008. Two hospitalizations. He was treated with neuroleptics: riset, sonapax, haloperidol. The second group of disability. We underwent a course of cytokines in the winter of 2015. Follow-up for 6 years. Mentally healthy. Married. Raises two children [9.].

The volume of the article does not allow for other examples. In general, we can summarize the following: the patients described above were treated only with cytokines, without the use of antipsychotics (Fig. 1, blue circle in the center). Against the background of treatment with cytokines, the use of antipsychotics is quite possible and often justified. Cytokines and antipsychotics have different points of application and, apparently, do not interfere with each other too much. We use antipsychotics very rarely and only in the initial period of treatment, since almost all patients come for maintenance therapy with two and sometimes three antipsychotics. Successful treatment results are still around 70%.



The blue circle in the center represents the astroglial networks. The genetic vulnerability of astrocytes in response to a change in the cytokine balance (green circle below) - reacts with a progressive deceleration of the general CSF dynamics in the glymphatic system of the brain. In the clinic, this looks like a reduction in the time and depth of delta sleep. The increasing toxicity of the cerebrospinal fluid modifies the astrocytes of the tripartite synapses and launches a second vicious circle symbolizing neural networks (yellow on the right) - this in different directions changes the sensitivity of neuroreceptors to dopamine, serotonin and other mediators. The red circle on the right symbolizes the death of oligodendrocytes and microglia in conditions of increasing autointoxication due to defective astroglial networks (blue circle in the center). All psychopharmacology is capable of acting only on interneuronal synapse (yellow circle on the right). Cytokines act on astrocytes and solve the therapeutic task of completely curing schizophrenia.

Picture 1



Picture 2

References

1.Snesarev P.E. Theoretical foundations of the pathological anatomy of mental illness. Moscow: Medgiz. 1950.372 P.

2.Voronov A.I. A new look at the pathogenesis and treatment of schizophrenia Academic Journal of Western Siberia 2018 №3 P.64-71

3. Voronov A.I. Pukhkalo K.V. Savin K.A. Reduction (reverse development) of defective symptoms as a result of long-term use of cytokines on the example of patients suffering from a simple form of schizophrenia (evidence-based psychiatry) Academic Journal of Western Siberia 2018 №6 P.19-33.

4. Kolomeets N.S. Intercellular interactions in the human brain in schizophrenia (ultrastructural analysis) Diss. Dr. biol. sci. M 2010 110 P.
5. Voronov A.I., Dresvyannikov V.L. Pukhkalo K.V. Schizophrenia. A new way of treatment Tyumen Medical Journal 2012 №1 P. 8-15.
6. Voronov A.I. A new way to treat schizophrenia. First successes and new tasks Academic journal of Western Siberia 2014 №6 P. 66-71.
7. A.E. Gareeva A modern view of the neurobiological hypothesis of schizophrenia. Journal of higher nervous activity 2019, volume 69, №4, P.437-455.
8. The Russian Federation. Patent for invention № 2484836 Method for the treatment of schizophrenia 2013.
9. Voronov A.I. Schizophrenia. Treatment with cytokines. Academic Journal of Western Siberia 2016 №6 volume 12 P.36-43.
10. Internet resource. Website https://schizophrenia8.ru/

Author's phone number + 7 913 912 89 07 E-mail voronov88888@yandex.ru