Chronic bacterial intoxication syndrome under the mask of CFS/ME

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We, Markov Igor S and Markov Artem I, present you the research work (the study/manuscript) "Chronic Bacterial Intoxication Syndrome under the mask of CFS/ME" about the never & nowhere-before-published unique original results of the almost 12-years (2009-2020) systematic clinical research of the true etiology of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME); about the new revolutionary previously unknown diagnosis Chronic Bacterial Intoxication Syndrome (CBIS) that gives such a long-awaited in-depth clinical understanding and discovery of the true basic etiological and pathogenetic causes of the long-known and worldwide-spread, but still etiologically mysterious CFS/ME; about clinical prompt diagnostics and unique successful methods of treatment of CBIS (treated more than 4500 patients: children-2160, adults-2340), hidden till the moment being under the mask of CFS/ME.

The search for the true origin and causes of CFS, which are globally associated mainly with the chronic EBV-infection, was started by our clinics back in 2005 after 5 years of unsuccessful attempts to achieve positive results with intensive anti-viral therapy. It took 10 long years, in order to the authors themselves could believe in what it seemed impossible to believe.

In all patients with typical features of CFS there was revealed a focus of chronic bacterial infection in the kidneys, which more often remained clinically locally asymptomatic and was called Nephro dysbacteriosis.

Bacteria toxins, that were extracted from urine, persisted in the kidneys for years and decades and caused severe often long-term intoxication and led to the development of a pathological condition that till the moment being is called CFS. So appeared a new previously unknown diagnosis chronic bacterial intoxication syndrome (CBIS) which etiologically and pathogenetically really reflects the diversified (symptomatically often multidisciplinary) clinic of this disease. The severity of intoxication often made the life of patients simply insufferable, therefore 28% of adults and even 1.4% of children experienced suicidal thoughts. Intoxication grade was confirmed by toxicological blood investigation.

The treatment of the patients with CBIS was successfully carried out by bacterial auto vaccines without traditional ("according to the Protocol") prescribing of antibiotics. Moreover, it was found that in at least 90% of patient's nephron dysbacteriosis and CBIS had developed precisely after thoughtless, expansive and aggressive antibiotic therapy, which often began in childhood. Taking into consideration in fact global treatment by antibiotics, how many people worldwide are really

suffering from nephron dysbacteriosis and CBIS, not receiving adequate treatment?

All clinical paths of removing the mask from CFS and of diagnostical transformation of CFS into CBIS is described consequentially and argumentally in the cycle of 9 reports/articles on clinical diagnosis, on bacteriological and toxicological diagnosis and treatment of CBIS. Below you find the first part of whole study "chronic bacterial intoxication syndrome under the mask of CFS/ME", namely Reports 1.-6. "Clinical diagnosis".

The second part of the study (Reports 7-9.) will contain data on bacteriological diagnosis (Report 7), toxicological diagnosis (Reports 8) and treatment of CBIS (Report 9). It's ready for publication and now some data are being translated in English.

And else: the current urgent situation with SARS-CoV-2 (Covid-19) is considered as an acute pandemic. But CFS/ME, correctly called as CBIS, which also do not recognize geographical boundaries and reap their deadly harvests during decades of proliferation in the world (the officially registered CFS number is up to 1% of global population, i.e. about 70-80 million people), can be courageously considered as a global infectious disease and a chronic pandemic, the fight against which remains no less urgent. And if humanity will be saved from Covid-19 by anti-SARS-CoV-2 vaccines, we believe that we have invented such a vaccine against disease called by us CBIS, hidden under the mask of CFS/ME.

Report 1: Clinical Diagnosis (beginning)

Abstract

Objective: Of the research was to establish the true cause of such a long-known disease as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), the etiology of which remained unclear. **Design:** clinical-diagnostic, included the search for ways to diagnose pathological state and to determine clinical features of a previously unknown disease, called chronic bacterial intoxication syndrome **(**CBIS**),** which has long been masked under the diagnosis of ME/CFS. The researches were prospective-retrospective and were longitudinal with long-term periodic supervision a certain part of the same patients for 1-10 years after establishing them diagnosis of CBIS and appropriate treatment. By achieved results effectiveness the researches had direct character, because undoubtedly improved the patient's life. The style of presentation of the material is narrative, not tedious.

Conditions: The researches were multicenter and conducted in ambulant conditions on the basis of 2 clinics specialized in the field of chronic infectious diseases with a full range of laboratory studies.

Participants: All patients (children up infancy and adults aged till 80 years) who seeked advice in clinics during 2009-2020 with complaints consistent with a diagnosis of CFS, which was previously diagnosed in almost a third of patients on former stages of examination and treatment.

Results: This first article opens a series of 9 reports of previously unknown diagnoses such as CBIS and nephrodisbacteriosis, febrile and pain attacks. It's planned the following sequence of

publications: reports 1-6 are about the clinical diagnosis. Report 7 deals with the bacteriological diagnosis and report 8 - with the toxicological diagnosis, which together confirm these pathological conditions. Final report 9 is devoted to the treatment of these pathological conditions without the traditional use of antibiotics in such cases in chronic bacterial infections - antibiotics on the contrary were the main cause of the emergence and progression of these diseases. During 2009-2020 the authors supervised 4500 immunocompetent patients (children 2160 or 48%, adults 2340 or 52%) with diagnoses of CBIS and nephrodisbacteriosis. It were determined the relations between the emergence of CBIS and previous more than once use of antibiotics, which received 4050/4500 (90%) of the patients. All 100% of adult patients with CBIS had 4-8 typical symptoms of a previously known diagnosis of CFS, which in almost a third of patients was determined in the previous stages of examination and treatment. In report 1 are provided well-known and historical facts of genesis of ME/CFS diagnoses, the main directions of investigations their etiological emergence cause, clinical symptoms defined by the Definition of 1994. Based on previous studies, the role of Epstein-Barr virus (EBV) in the emergence of CFS is proved as insignificant or even absent.

The known: Existence of a diagnosis ME/CFS with an unknown etiological cause.

The new: For the first time it's clinically determined and laboratory confirmed that under the mask of ME/CFS is hidden still unknown chronic bacterial intoxication syndrome (CBIS), which develops as inflammation of chronic usually locally asymptomatic bacterial infection in kidneys, called nephrodisbacteriosis.

The implications/Conclusions: It has been established the existence of such a clinically and nosologically separate disease as chronic bacterial intoxication syndrome (CBIS), which for a long time still camouflages under ME/CFS. CBIS develops as inflammation of chronic usually locally asymptomatic bacterial infection in kidneys (nephrodisbacteriosis) and is usually associated with severe bacterial endotoxicosis, as confirmed by appropriate toxicological blood investigation (see Report 8).

Key words: chronic bacterial intoxication syndrome (CBIS), nephrodisbacteriosis, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), antibiotics, Epstein-Barr virus (EBV).

Well-known Information: This article will talk about what seems familiar, but in fact remains completely unknown to the wide community of doctors and patients. Because the diagnosis in question formally and documentary as if does not exist. It is not mentioned about this in schoolbooks, manuals, and classifiers of diseases or elsewhere. But it exists clinically. Many patients, children and adults who suffered from this pathological state, are ill for years, suffer and wander around the offices, seek advice to specialists of various profiles to find the correct diagnosis, spend time and money. During this time, such patients are unsuccessful and "just in case" prescribed various courses of medicinal treatment without any positive result. Eventually, such patients finally lose hope and faith in doctors, in the perspective of recovery with the subsequent formation of anxiety-neurotic, depressive and senestopathic-hypochondriac disorders. Many of them come

under the supervision of infectious disease specialists, neurologists, psychiatrists and take for years antibacterial, antiviral and psychotropic medications. Over time they are assigned the definition of "difficult and inexplicable" patients or so-called "suffering travelers" [as described in the article "If a doctor has a computer soul" by Yarosh O.O. in the newspaper "Vashe Zdorovya" No.13 (297) dd. 20 February 1999, Kyiv, Ukraine - open public source].

So what is it about? From special and medical literature as well as from the Internet it's well known such a disease as chronic fatigue syndrome (CFS) - a disease characterized by constant fatigue that does not disappear even after a long good rest. This state has many different other names: systemic loads intolerance disease and benign myalgic encephalomyelitis (ME/CFS), post-viral asthenia syndrome, immune dysfunction syndrome. Clinically, it is almost impossible to distinguish the chronic bacterial intoxication syndrome (a term that nobody accepts the authors of this article has used to define this state of constant fatigue) from the usual name chronic fatigue syndrome. It seems to be the same disease, but with different names. Therefore, let's first turn to the history of the very name of such a disease as chronic fatigue syndrome.

Historical Information: Chronic fatigue syndrome is a diagnosis that is well-known from the special medical and popular science literature, and more recently from the Internet, about which many articles and books have been written. CFS is considered as a state of constant exhaustion, disability and rapid fatigue, which negatively affects the quality of life, lasts more than six months and is accompanied by numerous joint, infectious, neurological, mental and other symptoms. Before the onset of CFS most patients have a high professional efficiency and success. It is emphasized that CFS is a heterogeneous disease that is realized by different pathophysiological mechanisms, but manifests similar symptoms. The origin of CFS often remains unclear and is accompanied by a number of concomitant symptoms. Management tactics of such patients includes confirmation of his work disability, treatment of certain clinical manifestations, and in some patients - cognitive-behavioral therapy and exercise program with a gradual load increase.

The disease was so named after a local outbreak, which was assessed as an epidemic, in Nevada, USA in 1984. Dr. Paul Cheney, who practiced in the small town Incline Village on the shores of Lake Tahoe, had registered more than 200 cases of this disease. Patients experienced drowsiness, concomitant depression, mood swings and muscle pain and muscle weakness, fever. They were detected Epstein-Barr virus or antibodies to it, but also to other herpesviruses - HSV, VZV and CMV. Whether the cause of the disease was a viral infection or something else, e.g. a bad environmental situation, remains unclear. Similar outbreaks had been observed before: in Los Angeles in 1934, in Iceland in 1948, in London in 1955, and in Florida in 1956. The syndrome is not limited by any geographical or socio-demographic groups. In the USA chronic fatigue syndrome affects about 10 patients per 100,000 populations, and in Australia in 1990 sickness rate was even higher: 37 persons per 100,000 populations. It is noted that women suffer from CFS on the average three times more often than men, and the average age of patients is people in the range of 40-60 years.

Although approximately 25% of people consider themselves to have chronic fatigue syndrome, only

about 0.5-1.0% of people actually have symptoms that meet the criteria for CFS. The prevalence of CFS in the adult population is 0.006-3%. Although the term CFS was first used publicly in 1988, this disorder, which was accompanied by chronic fatigue, had been described at least since the mid-1700s, but again under various other names: general malaise, neurasthenia, chronic brucellosis, neurocirculatory dystonia, and so on. CFS was most often reported among young and middle-aged women, but it were reported cases in all age groups, including children, and in both sexes.

Everyone knows the familiar feeling of fatigue, which is usually perceived as a completely normal reaction of the organism to various external factors that affect our physical, emotional and mental state. But if the fatigue does not pass for weeks, especially after a good rest dreaming about, but on the contrary increases each day, there is a high probability that it is not just fatigue, but a pathological state. Someone estimated that about one in five adult patients (10-25%) seeking medical care at all complains of prolonged fatigue. In cases of inability to explain fatigue by a certain disease, it is suggested that it may be the chronic fatigue syndrome.

Terminology: According to the previous ICD-10 (approved at the 43rd session of the WHO in May 1990), CFS was considered in a number of neurological diseases (G93). Along with CFS, its secondary forms are distinguished in some neurological pathological states. Chronic fatigue accompanies such diseases as multiple sclerosis, Parkinson's disease, anterior moto neuron disease, chronic cerebral ischemia, stroke, post-polio syndrome (PPS) and others. And quite often fatigue is the main complaint of patients. Secondary forms of CFS are thought to be based on direct damage to the central nervous system and the influence of other factors indirectly related to the main disease. For example, depressive disorder, which often occurs due to any neurological disease.

The term and definition of CFS were first introduced by American scientists in 1988. In 1994 the definition of CFS was revised and already in an updated form it acquired international status. According to the definition of 1994, it takes at least 6 months of unexplained fatigue, which does not disappear and is not relieved after rest and significantly limits the level of daily activity. In addition to fatigue lasting at least 6 months, four or more of the following 8 symptoms should be present:

- Impaired memory or concentration of attention;
- Pharyngitis;
- Painful cervical or inguinal lymph nodes on palpation;
- Muscle painfulness or stiffness;
- Joint pain (without redness or swelling);
- Recurrent headache or change of its quality (type, severity);
- Sleep that does not bring a feeling of recovery (freshness, vitality);

- Increasing fatigue up to exhaustion after physical or mental effort lasting more than 24 hours.

Etiology: The etiology of CFS is still unknown. For this disease it's not determined specific infectious, hormonal, immunological or psychiatric causes. It has not been conclusively proven that among the many infectious agents proposed as causative agents of this disease (Epstein-Barr virus, cytomegalovirus, Lyme disease, candidiasis and many other potential infectious factors considered for this role) there are a direct and the only causative agent of CFS. Allergic markers and immunosuppression have also not been established. The large role as if played by macro- and micronutrient deficiencies, food allergies, excessive physical and mental stress, viral infections and much more others has not yet been evidentiary confirmed.

Some researchers also believe that the cause of CFS may be a change in the bacteria balance in the intestines. According to Columbia University (New York, USA), 90% of people with CFS have irritable intestines syndrome. And in 80% of them there is a deviation in the content of the following seven intestinal bacteria: Faecalibacterium, Roseburia, Dorea, Coprococcus, Clostridium, Ruminococcus, Coprobacillus. According to some other authors, CFS is the result of only psychiatric pathology: somatized disorders, "major" or atypical depressions. It has been suggested that the occurrence of CFS is associated with the development of neurosis of the central regulatory centers of the autonomic nervous system due to the activity suppression of the area responsible for inhibition processes. Although as known before there are no specific zones responsible for the processes of excitation and inhibition in the nervous system.

In 2009 scientists from the USA published an article describing the effects on the human body of the "chronic fatigue syndrome virus" that affects mice. After a few years these data were refuted because the virus could not be detected in the blood of the studied patients. However recently other biologists have announced their results. Their conclusion proved the presence of a previously unknown virus in the blood of patients: it seems to appear when the immune system is in a state of constant stress.

In January 2016 a group of British scientists published their research, according to which a chronic fatigue syndrome virus still exists and affects particularly teenagers. According to experts, more than 2% of teenagers in the UK have chronic fatigue syndrome. Typical symptoms of this disease are insomnia, fatigue, headache and frequent spasms.

In the absence of another, the infectious, namely viral theory of the origin of CFS is currently recognized the most convincing. According to this theory, the trigger factors for CFS may be Epstein-Barr virus, cytomegalovirus, herpes virus type 6, Coxsackie virus, hepatitis C virus, enteroviruses and retroviruses. The debut of CFS is often associated with acute respiratory flu-like illness with fever. The data on the high frequency of detection of herpesviruses and signs of their reactivation in patients with CFS are also considered convincing. The possibility of the existence of a still unidentified virus (most likely from the group of herpes viruses) that causes CFS is not completely ruled out, while other known viruses (EBV, CMV, HHV-6 etc.) can play only a secondary

role, reacting due to immune status disorders and supporting them.

Different observers at different times considered also other non-infectious causes of CFS:

- Chronic diseases that cause disorders of the immune system;
- Psychological and mental disorders - frequent depression, feelings of anxiety and fear, regular stress;
- Wrong way of life - lack of sleep, prolonged overexertion, insufficient insolation and/or lack of fresh air, hypodynamics, irrational daily routine;
- Eating disorders: starvation or overeating, malnutrition (hypo- or avitaminosis, lack of macro-and micronutrients);
- Environmental factors - residents of megalopolisis have a higher risk of chronic fatigue syndrome than others as the polluted environment affects the general state of the organism;
- Factor of unbalanced emotional and intellectual load in people with increased responsibility in the work activity: medical workers, air traffic controllers, railway operators etc.

Pathogenesis: Numerous reports indicate that both quantitative and functional minor immunological disorders are observed in CFS. Among the objective indicators it's described the decrease of immunoglobulins G (IgG) primarily due to G1- and G3-classes and appearance of abnormal IgG, the number of lymphocytes with phenotype CD3 and CD4, natural killers, increased level of circulating complexes and antiviral antibodies of various types, increased β-endorphin, interleukin-1 and interferon, as well as tumor necrosis factor, low levels of gamma-interferon in response to mitogens. Most patients with CFS have a decrease of the number and/or decreased function of natural killers. Thus it's believed that the change of the phenotype of immunocompetent cells and dysfunction of natural killers are a common manifestation of CFS. Also as factors of pathogenesis are discussed: the increased formation of lactic acid in response to physical activity, disturbance of transport of oxygen to fabrics, decrease of the number of mitochondria and their dysfunction at patients with CFS. However none of the detected deviations provides adequate sensitivity and specificity for the determination of CFS. However it's still believed that they emphasize the physiological legitimacy of the existence of CFS.

Relatives of patients with CFS have an increased risk of developing the syndrome that suggests the presence of a genetic component or a general predisposition to the influence of Eco pathogenic factors. Recent studies have reported some genetic markers that may be related with a predisposition to CFS. Some researchers believe that the etiology of the syndrome may ultimately be multifactorial, including genetic predisposition and influence of microbes as well as toxins and other physical agents and/or emotional trauma. Some reports note that the degree of L-carnitine deficiency is

directly related to the expression degree of symptoms of CFS. That is the less L-carnitine (and its esters) is contained in human blood plasma, the lower its work efficiency and worse health.

Clinic: The peak incidence of CFS occurs at the active age of 40-59 years. According to existing observations, women of all ages are more inclined to this disease and make up 60-85% of all patients. Children and teenagers suffer from CFS much less often than adults. The obvious features of CFS include severe pathological fatigue even during elementary loads and daily responsibilities, very often complete weakness. Sleep and rest do not bring relief and do not give the desired vitality. Subjectively patients may formulate the main complaint in different ways: "I feel myself completely tired", "I've constantly lack energy", "and I'm completely exhausted", "ordinary loads lead me to exhaustion". However active questioning allows understanding that patients separate their feelings from normal muscle weakness or feelings of despair.

Most patients subjectively assess their physical state before the disease as good or even excellent. From the anamnesis it can be objectively established that before the onset of CFS they were highly able to work and were successful in professional and personal life. The feeling of extreme fatigue appears suddenly and is usually combined with flu-like symptoms. The disease may be preceded by respiratory infections, bronchitis, vaccination and sometimes blood transfusions. Less often the disease has a graduated beginning and sometimes begins slowly over many months. After the onset of the disease patients notice that physical or mental exertions leads to an increase in fatigue feelings. Many patients believe that even minimal physical effort leads to significant fatigue and worsening of other symptoms, including increased headache, muscle and/or joint pain, memory impairment etc.

Pain syndrome is characterized by diffusion, uncertainty, the tendency to migrate pain. In addition to pain in muscles, which sometimes can resemble the fibromyalgia syndrome judging by intensity, and in joints, patients complain of headaches, sore throat, sore lymph nodes and abdominal pain. Immune changes include painful lymph nodes, recurrent sore throats, recurrent flu-like symptoms, malaise and hypersensitivity to foods and/or medications that have not previously caused such reactions.

In addition to the 8 main symptoms (according to the Definition 1994 of CFS) that are relevant as diagnostic criteria, patients may feel other manifestations, the frequency of which varies widely. Orthostatic hypotension and tachycardia, episodes of sweating, pale skin, sluggish pupillary reactions, constipation, accelerated urination (microuritization), respiratory disturbance (shortness of breath, airway obstruction or respiratory pain) are more often described. Many patients have a violation of temperature homeostasis: usually the body temperature is sub febrile with daily fluctuations and may be accompanied by episodes of sweating, repeated chills. This category of patients is usually weather-dependent and does not tolerate extreme changes in ambient temperature (cold, heat).

Approximately 85% of patients complain of decreased concentration, attention, memory impairment, but routine neuropsychological examination does not reveal a deficiency of cognitive function. Sleep disorders are represented by various symptoms: difficulty falling asleep, intermittent night

sleep, daytime drowsiness, at the same time polysomnography has variable results. In general, it is clinically recommended to distinguish fatigue from drowsiness and keep in mind that drowsiness can both accompany SFS and be a symptom of various other diseases, e.g. sleep apnea syndrome.

Almost all patients with CFS suffer from social maladaptation. Approximately one third of patients are unable to work and another third prefer part-time employment. CFS is often accompanied by depression. The average duration of the disease is 5-7 years, but can last more than 20 years. Often the disease is wavy, periods of exacerbation (deterioration) of the disease alternate with periods of relatively good health. Most patients experience partial or complete remission, but the disease usually returns.

CFS has generally a changing clinical picture, making it difficult to identify any its specific symptoms. However doctors distinguish the following most typical clinical signs:

- Lack of feeling of rest after a good night sleep;
- Headache which often returns for no apparent reason;
- Increased drowsiness during the daytime;
- Inability to fall asleep quickly even after strenuous physical work;
- Unmotivated irritation;
- Causeless bad mood;
- Frequent infectious diseases;
- Allergic reactions;
- Decreased memory and ability to concentrate;
- Pharyngitis;
- Inflamed lymph nodes in the neck and/or groin area;
- Incomprehensible muscle pain.

Diagnosis: Despite the fact that everything seems very simple, sometimes CFS is difficult to diagnose because its symptoms are similar to the symptoms of many other diseases. The criterion for diagnosing CFS, according to the Definition 1994 of CFS, is chronic fatigue lasting 6 months or longer and 4-8 major symptoms. CFS can be diagnosed only after the exclusion of alternative somatic and mental causes.

The diagnosis is made on the basis of characteristic features from the disease history in combination with the results of a standard physical examination and conventional laboratory tests. Sometimes

it may be useful to use criteria to detect the disease, but they are mainly a tool for epidemiological researches and less should be applied to individual patients.

Despite the existence of different opinions about the causes of CFS and the mechanisms of its development, all experts who have studied this problem are united in one thing: CFS does exist and is not a simulation of the disease (intentional simulation of symptoms). In 2019 the WHO recognized the preservation and even increase in recent years the actuality of the problem of CFS and recommended to provide additional researches and monitoring to establish clearer mechanisms of the emergence and development of this pathological state.

Materials and Methods

History of new diagnostic terms emergence: During almost 12 years (from 2009 to 2020) under our supervision and treatment were more than 5 thousand patients diagnosed with chronic bacterial intoxication syndrome (CBIS). The diagnostic term CBIS and other new terms related to this diagnosis began to be used since February 2009, when this diagnosis was first established [1], but their final understanding, interpretation and formulation took place throughout all observation period. 4500 immunocompetent (with HIV/AIDS absence) persons were included in the group of statistical processing of the observation results of random sampling method. There were 2160(48%) children from infancy up to aged 14 years, and 2340(52%) of adults (up to aged 80 years) that does not coincide with the existing reports about a predominant emergence of CFS in adults. Among adults there were 1287(55%) men, women - 1053(45%), i.e. women with CBIS were ill even slightly less often than men, in contrast to the known information that women with CFS get sick much more often (60-85%). Usually got sick people of the most working-able age: more than half of adults were between the ages of 30 and 50 - 1240 people (53%) that almost coincide with the peak age incidence of CFS which is reported to be at the active age of 40-59.

With a pre-established diagnosis of CFS to the clinic went almost a third of the adults who had been re-diagnosed with CBIS after investigation in the clinic. The diagnosis of CBIS for children in almost all cases was initially determined during examination and investigation in the clinic that explains the very low statistical percentage of CFS registration in children which is usually disguised under other diagnoses. There was not established dependence of CBIS from any risk groups, profession and place of residence, social status, heredity and genetic dependence. Only occasionally two or more members of the same family seeked advice with similar complaints, and while detailed clinical questionning there were revealed common and similar symptoms in them. However this had nothing to do with heredity, but reflected the development of nephrodisbacteriosis on the background of almost continuous prescription of antibiotics to different patients, including to members of one family.

However there was determined a clear dependence of the emergence of CBIS on previous antibiotics medication: anamnesis of 4050 patients (90%), children and adults, showed that they were repeatedly prescribed antibiotics with different mechanism of antimicrobial action. At the same time in almost two thirds of adults the first overload of the organism with antibiotics occurred in

childhood more often due to frequent colds and their purulent-inflammatory complications. These circumstances allowed suggesting the primary formation of a focus of chronic bacterial infection in the kidneys (nephrodisbacteriosis) which became the main cause of further CBIS, usually in the distant anamnesis. Some diagnostically unverified symptoms (intoxication shadows under the eyes, constantly increased sweating, etiologically undetermined anemia etc.) reflected further perennial smoldering of nephrodisbacteriosis with the subsequent clinically formed debut of CBIS in adult age after some provoking factor.

In almost a third of cases this factor was the use of antibiotics which were usually prescribed either after the emergence of a flu-like state 1-2 months before which was earlier often associated with the occurrence of CFS or for other reasons. But in the vast majority of cases an in-depth study of the anamnestic data for such a flu-like state revealed the following. Despite of following features as almost complete absence of catarrhal symptoms with a runny nose and cough, the diagnosis of "flu" established in the summer, fever to 39°C and above which could last almost monosymptomatically from 3-4 to 7-10 days and some others - patients had no manifestations of "flu" or "SARS". This was a incorrect diagnosis under which masked the typical for CBIS febrile attack that could usually be the first clinically manifest demonstration of an almost latent long-term course of nephrodisbacteriosis.

Now is probably the time to stop on the prehistory of origin of such terminological and diagnostic concepts as the syndrome of chronic bacterial intoxication (CBIS), nephrodisbacteriosis and some others, the origin of which had in some ways a certain mysterious and enigmatic color. Therefore it is worth to explain how this happened.

For a long time the onset of CFS of infectious origin, beginning with the first outbreak in 1984 in the Incline Village town, was most likely associated with chronic Epstein-Barr virus infection. Clinical manifestations of chronic EBV infection over the past almost 30 years various authors in different sources describe in the literature almost unanimously as follows, identifying them, in essence, with the clinic of CFS. ”Chronic active EBV-infection is characterized by a long recurrent course and the presence of clinical and laboratory signs of viral activity. Patients suffer from prolonged low-grade fever, weakness, sweating, often - pain in muscles and joints, skin rash, cough, difficult nose breathing, discomfort and sore throat, pain and heaviness in the right hypochondrium, previously uncharacteristic for this patient headache, dizziness, emotional lability, depressive disorders, sleep disorders, decreased memory, attention, intelligence, ability to work. Often there’re observed increased lymph nodes, hepatosplenomegaly of various severity. Often this symptomatology has wavy character”.

Also some pay attention to the appearance of frequent mostly bacterial infections of the nasopharynx, respiratory tracts, skin, gastrointestinal tract, genitals, urinary system which on the background of the usual antibiotic therapy in such cases either do not pass completely, or return very quickly. Some note that often this state develops after a sore throat, ARI, influenza-like illness of unknown etiology. Some emphasize that characteristically for this variant of chronic EBV infection also are persistence and duration of symptomatology-from six months up to 10 years or more. Some refer to laboratory

(indirect) signs of viral activity such as relative and absolute lymphomonocytosis, the presence of a small number of atypical mononuclear cells, rarely monocytosis and lymphopenia, in some cases - anemia and thrombocytopenia or even pancytopenia. Some report that repeating PCR-testing detects EBV in saliva and/or in lymphocytes of peripheral blood, without clarifying, unfortunately, the proportion of these findings and the number of detected viral DNA copies. Some notify that long-term remission in most patients can be achieved only in the case of "sustained suppression of viral replication". And finally some state that, as a rule, repeating in-depth examinations most of these patients with CFS do not allow to reveal other etiological causes of their bad state, except for chronic EBV infection.

It should be noted that for a long time the etiological role of EBV infection in the occurrence of CFS was proved on the basis of releasing antibodies to this virus by ELISA in patients with chronic fatigue, and especially in "high" titers. This widespread opinion and assessment of the possible role of chronic EBV infection in the development of certain pathological states in humans, including CFS, were formulated many decades ago. But very often there is till the moment being the same misinterpretation by practicing in the field of herpes viruses and in particular EBV-infection doctors and even by employees and professors of the relevant departments of medical universities and profile research institutes. However it must be admitted that it was originally also our opinion 25 years ago, when we orienting on world experience in this matter began an in-depth study of the clinical manifestations of chronic EBV-infection with laboratory confirmation of the diagnosis. Therefore it is not surprising that the new clinical vision and diagnostic interpretation of CFS also began with a reassessment of the role of Epstein-Barr virus in the occurrence of this disease.

Yes, all started namely with the Epstein-Barr virus. Initially in 1999 we finally proved that the levels/titers of IgG antibodies in chronic viral infections, including chronic persistence of EBV, independently from the degree of their increase do not confirm the activity of the virus and its etiological role in emergence of a certain disease, and therefore they cannot be a basis for prescribing antiviral therapy and a criterion for the effectiveness of such treatment [2]. In 2002 it was finally determined that the level of infection with Epstein-Barr virus in Ukraine is the highest among other herpes viruses and ranges from 46.5% to 79.4% in children of different age groups up to 94.2% - in adults [3]. Therefore the very presence of IgG antibodies to EBV, frequency of determination of which among adults in Ukraine increased to 98% over the next 10 years, indicates only on chronic EBV-infection and cannot be confirmation of the etiological role of this virus in the occurrence of CFS and other pathological states. In addition on the basis of serological survey of 911 patients with chronic EBV-infection during 1997-2001 it was stated that the notion of a "serologically active profile" that as if had to confirm its active stage, does not exist at all [3]. Therefore the only criterion for the replicative activity of the virus was accepted PCR-testing for EBV both blood and saliva. During 2000-2001 the replicative form of chronic EBV infection was detected in 230 patients, on this basis it was even compiled the original table "Clinical diagnoses and pathological states of patients with replicative forms of chronic EBV infection" which included more than 20 diagnoses and symptoms and the first 44 treated patients with CFS [4].

But further there was disappointment. Initially there was performed a thorough examination of patients with CFS for chronic EBV infection. And then after PCR-confirmation of its replicative stage, we carried out versatile appropriate treatment, using the most modern for that time antiviral drugs, developing various schemes of such treatment including drugs on the basis of acyclovir, ganciclovir, recombinant interferons, specific immunoglobulins etc. Till 2004 in the Vitacell Clinic were treated with the diagnosis CFS, associated with chronic EBV infection in the replicative activity stage, nearly 400 adult men and women. In all patients PCR revealed different amounts of viral DNA in saliva, and in about 5% - even in the blood that seemed to unequivocally confirm this diagnosis. After treatment which in most cases was provided in in-patient conditions with acyclovir or even ganciclovir intravenously, in almost all cases we managed to achieve, as our colleagues emphasized, "sustainable suppression of viral replication." Patients even noted an improvement in their well-being and general clinical state. It's hard now to say if it was a real improvement or it seemed only so. But, Yes, it is clear that there was the "but": many patients began to return with the same complaints as before the first treatment. Before the first, because in more than 50 cases the second course was given, and in some especially persistent or frightened patients - even three courses of antiviral treatment which they themselves insisted on. Unfortunately with the same limited positive clinical result or even with its complete absence. Although everything was done taking into account all existing for that time recommendations for the examination and principles of treatment of such patients. It's a pity, but it was necessary to do something with this "but".

Looking ahead it should be noted that on the basis of the PCR-results for EBV for more than 5500 immunocompetent children and adults with diagnosis chronic EBV-infection, received in the last 12 years at Vitacell Clinic and Markov Clinic, it was conclusively proven negligible or even absent role of this virus in the emergence of CFS. Moreover it can now also be emphasized that in immunocompetent individuals without HIV/AIDS, *chronic EBV*-infection has almost no general clinical manifestations and only in some limited cases could manifest clinically only in local forms, such as etiologically associated with EBV uveitis, non-specific ulcerative colitis, some rare forms of hematological and oncological diseases, possibly others. About this has to write consciously today a doctor who 20 years ago compiled a table of clinical manifestations of chronic EBV-infection and wrote the following: “Chronic EBV-infection is a multifaceted disease with almost universal damage of various organs and systems that run under different masks of other diagnoses” [4]. So the time and clinical experience make its adjustments to our today’s understanding of some prevalent diseases, viruses and pathological states that they cause which 25 years ago seemed completely stable.

During the next 5 years (since 2005) even PCR-positive forms of chronic EBV infection with a confirmed stage of replicative activity of the virus in patients with CFS symptoms were no longer treated with antiviral medicaments. Moreover observations had proved that up to 25% of children and 20% of adults almost constantly secrete the virus with saliva, while remaining clinically healthy. Moreover with the constant use in the Markov Clinic of quantitative PCR test-systems to determine DNA of EBV with a fairly low threshold of sensitivity (at 500 copies of DNA/ml) very often in patients with a determined very large number of copies of DNA of EBV in saliva from 500 thousand

up to several million (in isolated cases - more than 50 million copies of DNA/ml) any clinical manifestations of EBV infection were completely absent. And the positive results of PCR-tests after a few weeks without any treatment decreased to a small number of copies or even became completely negative.

That is with this infection a healthy virus secretion with saliva is widespread, due to which there is almost 100% pro-epidemicization of the population. Moreover why prescribe such treatment if the doctor himself has stopped believing in its success? So how can a patient believe in this success? So.

The light at the end of the tunnel was seen only in 2009. It is difficult now to remember where it came from, who the first patient was and how it came to mind to do so. And it was done that what before and probably still, none of doctors in search of the causes of the sometimes just awful state, in which are many children, women and men with CFS on the background of chronic EBV infection, never prescribed or did.

There were made elementary cultures of urine for bacteria. And not just urine, but warm urine, which according to our data, 2.5-2.7 times by itself increased the sensitivity of the method and the probability of a positive result of bacteriological examination, and here three times - three days in a row. And we began to do so first to all patients without exception with signs of CFS, and later - too many others with chronic recurrent viral and bacterial diseases and unclear or undetermined in etiological plan pathological states. And yet we found the answer on this difficult question that life itself posed.

And the answer was very simple (so often happens). From the urine we began end masse to excrete as if Saprophytic bacteria, our lifelong companions. Bacteria that had to live naturally in our intestines and work there productively, providing human life. But which, apparently by mistake, but purposefully settled in the kidneys. Most often they were enterococci and *enterobacteria-Escherichia coli*, *Klebsiella*, Proteus, Enterobacteriaceae, *Morganella*, Acinetobacteria, Hafnia, Seratia and others, in no single cases - Staphylococcus and Streptococcus, less often - Nosocomial Pseudomonas aeruginosa.

The society, it has been found that being a long time in the kidneys, often from an early children age, usually after no single use of antibiotics, these bacteria do not initially cause local inflammatory processes such as pyelonephritis, but can cause very severe and debilitating intoxication. This may be due to the initially low virulence of the bacteria and/or the preservation of the protective barrier function of the local immunity of the renal mucosa. Just they caused the intoxication emergence which had all clinical features of CFS, but intoxication, in the usual sense of this word, was never associated with chronic fatigue. Thus in 2009 in our terminology for the first time appeared two new previously unknown diagnoses: nephrodisbacteriosis and chronic bacterial intoxication syndrome (CBIS), to the final understanding and interpretation of which there was the way of clinical observations and reflections lasting more than 10 years. At present under these terms we understand the following.

The Implications/Conclusions:

1. It has been established the existence of such a clinically and nosologically separate independent disease as chronic bacterial intoxication syndrome (CBIS) which still runs under the mask of ME/CFS.

2. CBIS develops on the background of ignition of chronic bacterial usually locally asymptomatic infection in kidneys, called nephrodisbacteriosis, and is usually associated with severe bacterial endotoxicosis, confirmed by appropriate toxicological blood tests, which will be reported in Report 8 about.

3. In 2009-2020 there were monitored at the Vitacell Clinic and the Markov Clinic 4500 immunocompetent (in the absence of HIV/AIDS) patients diagnosed with CBIS including 2160 children (48%) and 2340 adults (52%) that did not coincide with the existing reports about the predominant occurrence of CFS in adults. Among adult men there were 1287 (55%), women - 1053 (45%), i.e. CBIS-women were ill even slightly less often than men, in contrast to the known information that CBIS-women get sick much more often (60-85%).

4. It was not determined dependence of the occurrence of CBIS on being in any risk groups, profession and place of residence, social status, heredity and genetic dependence. Only sometimes two or more members of the same family had similar complaints, and while detailed clinical questioning there were revealed in them common and similar symptoms. However this had nothing to do with heredity, but reflected the development of nephrodisbacteriosis on the background of almost continuous prescription of antibiotics to different patients, including to members of one family.

5. There was established a clear link between the occurrence of nephrodisbacteriosis and CBIS and the previous antibiotic use: it was found in anamnesis of 4050/4500 (90.0%) patients that they were prescribed and they usually not once took before antibiotics of different groups. At the same time in almost two thirds of adults the first overload of the organism with antibiotics occurred in childhood more often due to frequent colds and their purulent-inflammatory complications. In almost a third of cases the onset or exacerbation of symptoms of CBIS also occurred after taking before (from a few weeks to 1-2 months) just antibiotics.

6. Based on the results of previous (during the last 12 years, 2009-2020) PCR-tests for EBV of more than 5500 immunocompetent children and adults diagnosed with chronic EBV-infection, it was established the insignificant or even absent role of this virus in the emergence of CFS. It was emphasized attention on the presence of healthy EBV-virus secretion with saliva in almost a quarter of chronically infected children and 20% of adults who remain herewith clinically healthy and do not require at all antiviral treatment.

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Report 2: Clinical Diagnosis

Abstract

Objective: Of the research was to establish the true cause of such a long-known disease as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), the etiology of which still remained unclear. **Design:** clinical-diagnostic, included the search for ways to diagnose such pathological state and to determine clinical features of a such previously unknown disease, called chronic bacterial intoxication syndrome (CBIS), which has long been masked under the diagnosis of ME/CFS. The researches were prospective-retrospective and were longitudinal. The style of presentation of the material is narrative, not tedious.

Conditions: The researches were multicenter and conducted in ambulant conditions on the basis of 2 clinics specialized in the field of chronic infectious diseases with a full range of laboratory studies.

Participants: All patients who seeked advice in clinics during 2009-2020 with complaints consistent with a diagnosis of CFS, which was previously diagnosed in almost a third of patients on former stages of examination and treatment.

Results: All patients underwent a general clinical diagnostic, biochemical, microscopic examination. In terms of differential diagnosis, almost all patients underwent ELISA and PCR studies (real-time) for all herpes viruses, especially EBV, according to clinical indicators - for Borrelia and other viral and bacterial infections. Almost all patients underwent examination of immune status with the determination of the cell unit by flow cytofluorimetry. According to clinical indicators there were additionally determined markers of autoimmune diseases, autoimmune hepatitis, allergies (general and specific IgE), tumor markers, hormones etc. Bacteriological confirmation of the diagnosis was performed by inoculating morning warm urine three times (three consecutive days) using the appropriate devices/tests Diaslide® DS-101 and DS-105 (Novamed, Israel) with applied nutrient media CLED agar, McConkey agar and chromogenic agar UriSelect (see Report 7). The toxicological diagnosis was confirmed by a blood test using the "Toxicon" diagnostic system (see Report 8). According to clinical indicators patients underwent instrumental examination: ultrasound, X-ray, MRI and CT, ECG, EEG etc.

Report 2 provides terminological definitions of previously unknown diagnoses such as chronic

bacterial intoxication syndrome, nephrodisbacteriosis, febrile attack and pain attack. In the general table of clinical manifestations of CBIS there were identified more than 70 symptoms and pathological conditions, which were conditionally divided into separate groups depending on the clinically dominant toxic effects on certain organs and systems: general toxic, mainly neurotropic (including peripheral neuropathies: sensory, motor, autonomic and vasotropic, autonomous, some others and neuralgic) as well as psychotropic, dermatotropic, arthromyotropic and ophthalmotropic.

The known: the existence of a large list of symptoms that were identified with the diagnosis of myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) with an unknown etiological cause.

The new: for the first time there were clinically identified more than 70 symptoms and pathological states of previously unknown diagnosis of chronic bacterial intoxication syndrome (CBIS) which were conditionally divided into 6 separate groups depending on the clinically dominant toxic effect on certain organs and systems. For the first time there was given a terminological interpretation of such hitherto unknown diagnoses and pathological states as nephrodisbacteriosis, chronic bacterial intoxication syndrome, febrile attack and pain attack.

The implications/Conclusions: On the basis of clinical observation and laboratory examination in 2009-2020 of 4500 sick children (2160 or 48%) and adults (2340 or 52%) there was formulated and presented clinical and terminological interpretation of such previously unknown nosologically separate independent diagnoses and pathological states as chronic bacterial intoxication syndrome (CBIS), nephrodisbacteriosis, febrile attack and pain attack. Clinical manifestations of the effect of bacterial toxins on the human body in cases of CBIS were conditionally divided into separate groups of symptoms, syndromes and pathological states, clinically combined by lesions of separate organs and systems.

Key words: chronic bacterial intoxication syndrome (CBIS), nephrodisbacteriosis, febrile attack, pain attack, clinical focus of bacterial toxins, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Terminological definition of new diagnoses and pathological states:

Nephrodisbacteriosis© - Is a locally asymptomatic (without features of inflammatory process) long-term focus of chronic bacterial infection in the kidneys, which is usually formed by ascending path and initially leads to the development of distant from kidneys features of CBIS and almost always precedes the debut of the clinically manifest pyelonephritis.

Under the ascending path it was understood an autoinfection by household contact with bacterial pathogens, primarily - enterococci and enter bacteria, which occurs daily in all children and adults, women and men while maintaining the most ideal sanitary and hygienic conditions and which has nothing to do with sex and sexually transmitting infections. The period of persistence of bacteria in the kidneys in children lasts for many years, and in adults - perhaps decades (usually from infancy and early childhood). Just nephrodisbacteriosis leads to the development of CBIS and is a mandatory first step in the subsequent occurrence of clinically manifest pyelonephritis. Therefore the diagnosis

of acute pyelonephritis, taking into account the established fact of existence of nephrodisbacteriosis, in terms of etiology and pathogenesis would be better considered as the first debut of chronic primary latent delayed pyelonephritis on the background of long-term nephrodisbacteriosis. It should be noted that not every nephrodisbacteriosis ends by the development of pyelonephritis: under certain circumstances it can occur in 10-15% of cases, although – possibly more often. The diagnosis of nephrodisbacteriosis is laboratory confirmed bacteriologically by cultural excretion from urine (preferably warm) of urinocultures of enterococci and various enterobacteria (more often - Escherichia coli), in many cases - staphylococci and streptococci, less often - nosocomial Pseudomonas aeruginosa.

Chronic bacterial intoxication syndrome© (CBIS) is a pathological state caused by endotoxicosis which develops on the background of a chronic bacterial infection in the kidneys (nephrodisbacteriosis or pyelonephritis) and causes clinically multi-vector manifestations of toxic damage of certain organs and systems of the organism, namely: generally toxic as well as mainly neurotropic, psychotropic, dermatotropic, arthromyotropic, ophthalmotropic and possibly others.

The diagnosis of CBIS, which had almost the same clinical signs as the previously known CFS, was confirmed by a toxicological blood test using the "Toxicon" diagnostic system developed by a group of Ukrainian scientists and clinicians led by Ukraine's chief pediatric toxicologist Borys S.Sheiman. Under this program there were examined more than 2000 children and adults diagnosed with CBIS. All patients, without exception, were diagnosed with endotoxicosis, mostly severe, rarely moderate, usually of bacterial origin with computer-programmed confirmation in most cases of a selective vector of toxic lesions of separate organs and systems, which almost coincided with the clinical manifestations of the disease. A toxicological blood test, the results of which will be presented in Report 8, was considered as a laboratory confirmation of the diagnosis CBIS. But there was also bacteriological confirmation, as well as clinical, which was proved by the results of appropriate treatment of these patients.

With the clinical manifestations of CBIS there were closely related such previously undefined states and correspondingly terms as febrile attack and pain attack.

Febrile attack © - A sudden temperature of toxic origin with an unexpected rapid and usually short-term increase from 38°C to 40°C in a clinically healthy child or adult and almost monosymptomatic (without the development of local symptoms of inflammation), which appears without predictors and fairly quickly passes without treatment and undesirable clinical consequences.

Pain attack © - rapid development in patients with nephrodisbacteriosis and CBIS of pain of various locations (such as trigeminitis, solaritis, intercostal neuralgia, headache, cardialgia, joint and spine pain, muscle pain, pelvic pain etc.) of paroxysmal and often intolerable nature, usually without the development of inflammatory processes, more often prolonged recurrent course.

Materials and Methods

All patients except for toxicological underwent also generally clinical examinations, which included general analyzes of blood, urine, feces etc., according to clinical indicators - biochemical examination (biochemical analyzer Beckman Coulter AU480, USA) of liver and kidney samples, protein fractions and rheumatic tests, glucose and glycated hemoglobin, lipid metabolism, vitamins, trace elements etc. Almost all patients in terms of differential diagnosis underwent ELISA and PCR testing (in real-time) for herpes viruses (HSV 1/2, VZV, EBV, CMV, HHV-6, HHV-7, HHV-8), according to clinical indicators – for Borrelia, other viral and bacterial infections. Almost all patients underwent examination of immune status with the determination of: cell unit by flow cytometry method with immunophenotyping of peripheral blood cells (flow cytofluorimeter CytoFLEX, Beckman Coulter, USA), immunoglobulins IgA, IgM, IgG, systems of complement C3 and C4, phagocytosis and circulating immune complexes. According to clinical indicators additionally - markers of autoimmune diseases, autoimmune hepatitis, allergies (general and specific IgE), tumor markers, hormones, microscopic examination of urogenital smears, prostate juice, sputum, nasal secretions. All patients were examined bacteriologically by cultural method using appropriate nutrient media. In all cases there were made sowing for bacteria of urine and nose and throat swabs, according to clinical indicators - from the skin, conjunctiva, gums, urethra, cervical canal, vagina, prostate secretion, ejaculate, secretions from wounds and fistulas.

Bacteriological confirmation of the diagnosis of nephrodisbacteriosis and correspondingly CBIS was routinely performed by sowing morning warm urine three times (three days in a row), which was usually performed at home using the appropriate testing devices Diaslide® DS-101 and DS-105 (Novamed, Israel) with applied on them nutrient media CLED agar, McConkey agar and chromogenic agar UriSelect. In cases of culture growth of microorganisms, they were re-inoculated on Petri dishes with such nutrient media as meat peptone agar (MPA) with the addition of 5% blood, Endo medium, Saburo agar, Mueller-Hinton agar (to identify bacteria of the genus Pseudomonas) and some others and it was continued the standard procedure of identification of isolated cultures. Urine for bacteriological examination was obtained naturally without the use of invasive method of bladder catheterization. According to clinical indicators patients underwent instrumental examination: ultrasound, X-ray, MRI and CT, ECG, EEG etc.

Results and Discussion

"Good day… Tired… Tired of going to the doctors… Tired of being treated… HELP !!! This is the last hope. "It is with these words, like a cry of the soul, very often began a virtual consultation via the Internet or a consultation in the clinic.

The clinical manifestations of CBIS were the most various, as it was constantly noted in CFS. The clinical vectors of the pathological action of bacterial toxins hidden in the kidneys resembled those arrows that, as in a children's Russian fairy tale, flew in different directions. We will remind briefly to those who forgot this tale, or did not know at all. The father-king called three sons and declared

that it was time for them to choose wives. And for this he ordered to shoot in different directions: where the arrow falls, there is fate. The arrow of the eldest son fell into the boyar's court, the middle - into the merchant's court, and the youngest - into the swamp, where the princess-frog lived. It was a beautiful fairy tale, so imaginative - it has not disappeared from memory for more than 60 years.

So in our history, when the arrows of those toxins that cause CBIS flew in the direction of various organs and entire systems of the sick person organism. But it is difficult to say where the first arrow can hit, where the second, where the others. Therefore we simply follow the clinical experience which shows that the manifestations of bacteria toxins effect (chronic focus of which was formed in the kidneys) on the human organism can be conditionally divided into the following groups of symptoms, clinically combined by lesions of separate organs and systems: generally toxic and mainly neurotropic, including peripheral neuropathies (sensory, motor, autonomic and vasotropic, autonomous), some others and neuralgic, separately - psychotropic, dermatotropic, arthromyotropic and ophthalmotropic. Depending on the main direction of toxins action that was usually confirmed by toxicological blood examination, in the clinical picture were dominated just those or other features of the disease. The following Table 1 describes the clinical manifestations of CBIS which there were counted more than 70 in total and which we observed in 4500 sick children and adults.

Table 1: Clinical manifestations of chronic bacterial intoxication syndrome (CBIS) in children and adults (n=4500).

Clinical Manifestations	Children (n=2160 or 48%)			Adults (n=2340 or 52%)
	Of first 3 years aged (n=540 or 25%)	From 3 to 7 years (n=750 or 34, 7%)	From 7 to 14 years (n=870 or 40, 3%)	
Generally Toxic:				
- weakness, increased fatigue	-	112 (15 %)	462 (53 %)	2340 (100 %)
- reduced work efficiency	-	-	-	2340 (100 %)
- reduction of tolerance to physical and sports activities	-	-	131 (15 %)	1848 (79 %)
- violation of vital energy	-	-	105 (12 %)	2223 (95 %)
- drowsiness, sleep disorders	-	-	191 (22 %)	2246 (96 %)
- "life in bed"	-	-	61 (7 %)	1755 (75 %)
- headache	-	68 (9 %)	279 (32 %)	2106 (90 %)
- subfebrile	243 (45 %)	398 (53 %)	565 (65 %)	1778 (76 %)

- febrile attacks	205 (38 %)	263 (35 %)	253 (29 %)	562 (24 %)
- intoxication shadows, swelling under the eyes	189 (35 %)	428 (57 %)	592 (68 %)	1849 (79 %)
- decrease or sudden body weight loss	-	-	-	1217 (52 %)
- developmental delays	135 (25 %)	128 (17 %)	78 (9 %)	-
- amimia	-	38 (5 %)	279 (32 %)	1427 (61 %)
Neurotropic Toxins. Peripheral Neuropathies (sensory-motor):				
- paresthesias in the fingers, palms, toes, feet	-	-	61 (7 %)	1568 (67 %)
- loss of balance and coordination of movements	-	-	-	421 (18 %)
- complications while driving a car	-	-	-	77/515 (15 %)
- complications when walking	-	-	18 (2 %)	281 (12 %)
- muscle weakness	-	-	18 (2 %)	211 (9 %)
- local cramps and muscle twitching	-	-	35 (4 %)	328 (14 %)
Autonomic Neuropathies and Vasotropic Toxins:				
- VSD	-	-	200 (23 %)	2200 (94 %)
- dizziness	-	-	270 (31 %)	1802 (77 %)
- tachycardia / bradycardia	-	-	157 (18 %)	1755 (75 %)
- increased heart rate	-	-	122 (14 %)	1638 (70 %)
- blood pressure drops	-	-	61 (7 %)	1521 (65 %)
- "hot flashes", a feeling of heat	-	-	-	1638 (70 %)
- spasms of peripheral vessels with freezing of the extremities	-	-	44 (5 %)	1895 (81 %)

- acute cerebrovascular spasm (by type of transient cerebrovascular accident)	-	-	-	70 (3 %)
- sympathoadrenal crises	-	-	-	280 (12 %)
- increased sweating	260 (48 %)	278 (37 %)	470 (54 %)	1825 (78 %)
Autonomous Neuropathies				
- nausea, vomiting, bloating after eating	-	83 (11 %)	122 (14 %)	444 (19 %)
- constipation and diarrhea	-	?	87 (10 %)	258 (11 %)
- disorders of the urinary system	49 (9 %)	240 (32 %)	218 (25 %)	680 (29 %)
- disorders of the genital area	-	-	-	296/1287 (23%)
- blurred vision	-	?	35 (4 %)	211 (9 %)
Some Other Manifestations of Neurotropic Toxins				
- tics	-	53 (7 %)	148 (17 %)	70 (3 %)
- arachnoiditis	-	-	-	374 (16 %)
- epileptic seizures	16 (3 %)	60 (8 %)	44 (5 %)	?
Neuralgia				
- trigeminal nerve	-	-	-	16 (0,7 %)
- occipital nerve	-	-	-	9 (0,4 %)
- external cutaneous nerve of the thigh (paresthetic meralgia or Roth disease)	-	-	-	12 (0,5 %)
- intercostal neuralgia	-	-	-	24 (1,0 %)
- abdominal pain (by type of solaritis)	-	-	3 (0,34 %)	7 (0,3 %)
- chronic pelvic pain	-	-	-	28 (1,2 %)
- chest pain	-	-	-	889 (38 %)
- heartache	-	-	70 (8 %)	1264 (54 %)

- pain in the lungs when breathing	-	-	9 (1 %)	281 (12 %)
Psychotropic toxins				
- asthenic syndrome	-	210 (28 %)	557 (64 %)	2340 (100 %)
- rapid exhaustion	-	150 (20 %)	478 (55 %)	2340 (100 %)
- deterioration of memory and logical thinking	-	-	340 (39 %)	1848 (79 %)
- decreased mental abilities	-	-	131 (15 %)	1264 (54 %)
- decrease in concentration, attention	-	135 (18 %)	279 (32 %)	1872 (80 %)
- reduction of life motivations, interest to the surroundings	-	-	157 (18 %)	2059 (88 %)
- apathy	-	-	122 (14 %)	1919 (82 %)
- phobias	-	90 (12 %)	218 (25 %)	1708 (73 %)
- panic attacks, depression	-	-	78 (9 %)	1732 (74 %)
- suicidal thoughts	-	-	12 (1,4 %)	655 (28 %)
- depersonalization / derealization syndrome	-	-	-	12 (0,5 %)
- manic-depressive syndrome	-	-	-	19/2340 (0,8%)
- appeal to a psychiatrist	-	-	44 (5 %)	1264 (54 %)
- taking antidepressants	-	-	18 (2 %)	725 (31 %)
Dermatotropic Toxins				
- itching of the skin and mucous membranes	-	-	148 (17 %)	1030 (44 %)
- brittleness and damage to the nails	-	-	11 (1,3 %)	912 (39 %)
- burning and "sand" in the eyes	-	-	70 (8 %)	1334 (57 %)
- a feeling of lump in the throat	-	-	24 (2,7 %)	1217 (52 %)
- prolonged reflex cough	38 (7 %)	143 (19 %)	218 (25 %)	679 (29 %)
- increased hair loss and alopecia	-	-	26 (3 %)	1240 (53 %)

- bacterial toxicoderma	222 (41 %)	398 (53 %)	392 (45 %)	889 (38 %)
Arthromyotropic Toxins				
- joint pain	-	113 (15 %)	270 (31 %)	1100 (47 %)
- reactive arthritis	-	73 (9,7 %)	157 (18 %)	540 (23 %)
- Reuters syndrome	-	-	-	12 (0,5 %)
- spine pain	-	-	104 (12 %)	1404 (60 %)
- muscle pain	-	-	44 (5 %)	585 (25 %)
- fibromyalgic syndrome	-	-	-	35 (1,5 %)
Ophthalmotropic Toxins				
- conjunctivitis	-	-	18 (2 %)	211 (9 %)
- uveite	-	3 (0,4 %)	7 (0,8 %)_	14 (0,6 %)
- retrobulbar visual nerve neuritis	-	-	-	5 (0,57 %)
- diplopia	-	-	-	7 (0,3 %)

Comparing the clinical symptoms observed in adult patients with CBIS with the main 8 symptoms of CFS (which, according to the Definition of 1994, there have to be at least 4 to diagnose CFS), the following should be noted. Among 2340 adult patients with CBIS at least 4 main symptoms in various combinations were found in all 100% of cases, 5 - in 2153 (92%), 6 - in 1849 (79%), 7 - in 1732 (74%) and all 8 - in 1240 (53%). This could most likely indicate that under normal circumstances all these patients should be diagnosed with a previously known CFS of unknown origin etiology.

Clinical manifestations of toxins of general toxic action caused the most typical symptoms of the disease, with which CFS was previously associated. Rather gradually (in almost 80% of cases) rather than suddenly, 100% of adult patients had a feeling of unexplained gradually increasing fatigue, which did not correspond in its intensity to the previous physical or mental load and did not disappear after rest. Although in some cases, when CBIS was dominated by a febrile attack with hyperthermia, patients could name not only the day but even the hour of disease emergence. In children aged 7 to 14 years, almost half of the patients, 462 (870) or 53%, noted increased weakness and fatigue. In preschool children such a complaint seemed to be atypical, but apparently only due to the child's incomplete understanding of what is happening to its and what it looks like. Although mothers of these boys and girls noted their unusual behavior: in the midst of lively play, their restless children suddenly for a few minutes begged "on the hands" or fell on the bed with their heads on a pillow, as if forced to rest, that is uncharacteristic for children of this age, who can play without a break from sunrise to sunset.

Normal physical work, which a person performed at work or at home the day before without even

noticing it, figuratively speaking singing, became difficult and unbearable for 100% of patients. This was especially noticeable for patients of professionally active age, who before the emergence of CBIS were characterized by high work efficiency, professional and life perseverance, creative productivity and were successful in their professional activities and in life in general. After the onset of the disease, patients of creative work lost all interest in their favorite or most urgent activities, which before they could do 24 hours a day: stopped doing dissertations, write a book or music, draw or embroider, prepare for personal exhibitions, model shows etc. In 1848 (2340) or 79% of adult patients, tolerance to physical, sports and mental loads decreased significantly, while in school-age children - only in 131 (870) or 15% of cases. One 25-years-old Olympic cycling champion said surprised: "I don't understand what's going on: I used to be able to pedal 20 hours a day without getting tired, but now I'm completely exhausted in 2 hours". Direct speech in other patients sounded quite disappointing: "as if I have been replaced", "I do not recognize myself", "I have no strength", "I just force myself to do at least something", "I do not understand: is it me?" a mother about her 14-years-old son:" barely crawls out of school".

Besides pathological fatigue, 2223 (2340) or 95% of adults (among school-age children, mostly teenagers - 105/870 or 12%) experienced a decrease of vitality, energy from a minor level to so palpable that bordered with complete exhaustion: the inability to raise eyelids , get out of bed, bring a spoon to its mouth, comb hair, dress oneself etc. Here is how some patients described themselves in this state: "I feel myself like a balloon from which air was released", "as if a battery inside me got empty", "I'm de-energized", "I was pumped with energy", "I'm like soaked pasta ","I don't even have the strength to sneeze "," I'm so exhausted that I can't even lift a spoon, it seems so hard to eat borscht "," I woke up in the morning, combed my hair - and my strength ran out ", a 41-years-old woman says: "I feel myself like an old grandmother".

Gradually a headache could join the predominant fatigue and decrease of vital energy, which constantly increased until exhaustion after any even slight physical or mental effort. This pain which came back again and again, almost without disappearing day or night, was constantly felt by 2106 (2340) or 90% of adults, almost a third of school-age children - 279 (870) or 32%, and sometimes even children over 3 up to 7 years - 68 (750) or 9%. But although this symptom in children did not seem to occur very often, in some cases in teenagers (mostly during puberty) it could become the main constant dominant complaint. Such a debilitating constant headache, which almost did not subside even after painkillers, forced parents in search of the cause of this uncertain condition to repeatedly turn to neurologists, other doctors, re-perform MRI and CT of the brain, afraid of reports from the Internet about a possible similar course of brain tumors and go through terrible days, months and even years, worrying and worrying about the future of his/her son or daughter.

Sometimes the headache was paroxysmal in nature, could appear after some external provoking factors (e.g. hot shower, stay in the cold or in the stuffy room, plant or animal odors etc.), lasted for many years and reminded, especially in women, a typical migraine, which they already knew and agreed to continue to fight it without overcoming it and to endure it forever. Incidentally complaints of paroxysmal headaches could sometimes be heard from young men. That is why it was amazing

for both patients and their doctor, when such constant attacks of pain, which before could not be treated by any modern methods, completely disappeared after treatment of chronic bacterial infection in the kidneys that confirmed the toxic nature of its origin.

Almost all adult patients with CBIS (2246/2340 or 96%) noted a variety of sleep disorders: difficulty falling asleep, inability to fall asleep after hard physical work or prolonged exercise, not sound sleep at night, waking up early with inability to fall asleep again or morning weakness when waking up, when "eyes do not open" and "eyelids as if glued together", irresistible daytime drowsiness (direct speech of a man of 37 years: "I go on the street, 12 o'clock in the afternoon, I feel that I fall asleep, eyes by themselves close, think at least for a few minutes just to fall asleep"). Sometimes on the contrary - a long full night's sleep, which did not bring a feeling of rest, recovery, freshness and vigor ("I wake up in the morning - and no strength"). Almost three-quarters of adults (1755/2340 or 75%) described their condition as "living in bed": when a person had no natural desire to leave the bed in the morning, he felt more comfortable in a horizontal position, with minimal exercise, constantly being in a state half-asleep. Although usually this condition did not last a lifetime and after a while could either weaken, or even disappear completely. Among school-age children minor sleep disorders were much less common: only 191 (870) or 22% of schoolchildren noted it, among them 61/870 children (7.0%) called their condition "life in bed." In almost a third of cases (61/191 or 31.9%) teenagers parents agreed that their children's behavior corresponded to their perceptions of their state.

One of the typical manifestations of CBIS which often dominated in the clinical picture of the disease, was a violation of temperature homeostasis. More than in half of children and two thirds of adults with CBIS (among adults - 1778/2340 or 76%, school-age children - 565/870 or 65%, children aged 3 to 7 years - 398/750 or 53%, the first 3 years of life - in 243/540 or 45%) there was a prolonged daily sub febrile, usually with periods of temporary normalization of temperature (often before bedtime and in the morning). Such sub febrileness caused constant psychological fatigue even more than physical suffering: due to the unknown cause of its occurrence, it led particularly vulnerable patients to complete exhaustion, forcing them to grab the thermometer again and again. Attempts of a physician, embarrassed by the lack of good reasons for such persistent sub febrile, to explain fever in general terms about "disturbances in the center of thermoregulation in the brain" or "thermoneurosis" usually did not inspire confidence in patients and forced them to look for another more plausible cause. For many patients chronic tonsillitis was called as a cause of sub febrile. Very often especially after the excretion of Staphylococcus aureus from the throat and the complete ineffectiveness of antibiotic treatment, in order to get rid of fever, it was recommended to remove the tonsils, "because there is no other way." And in vain: tonsillectomy "in connection with sub febrile", with all possible undesirable consequences of surgical intervention, was not necessary in these cases, although it was made for 120/2340 (5.1%) adults and 55/870 (6.3%) schoolchildren. But due to obvious reasons, this had almost no positive clinical effect on the temperature that maintained after surgery in 114/120 (95.0%) adults and 51/55 (92.7%) children.

But there was, unfortunately, a more physically exhausting variant of the temperature disorders with fever, which we observed in 562/2340 (24%) adult patients and more than a third of children: under the age of 3 - in 205 (540) or 38%, in preschool age - in 263 (750) or 35% and in school age - in 253 (870) or 29% and which we called a febrile attack. In these cases, which we observed almost 1.2-1.5 times more often in children than in adults, without any warnings and signals from an externally healthy organism, the temperature critically quickly reached usually 39-40°C. The fever lasted in most cases for 1-2 to 5-7 days and clinically was almost monosymptomatic: only occasionally adult patients noticed a short-lived concomitant headache, slight chills and fever and muscle pain. Children could not notice the high temperature at all, continuing their children's games and entertainment. The fever had usually intermittent character with a decrease of temperature during the day to normal and a new increase, only in some cases - remittent or attenuating with a daily change within 1°C, which however did not decrease to normal. This temperature as if came without a declaration of war and have left without a declaration of capitulation. Fever in case of nephrodisbacteriosis and CBIS was usually hardly treated by antipyretic drugs and almost did not respond to the use of antibiotics, that is understandable - because it was mostly not inflammatory but toxic.

In some cases (in 70/2340 adults or 3% and 25/2160 children or 1.1%, in total - in 95/4500 or 2.1% cases of CBIS) high fever at the level of 38-40°C continuously lasted daily for 1 to 3 months (in some cases - several years), that led to significant physical and emotional exhaustion and already required the exclusion of cancer, autoimmune and systemic diseases, HIV/AIDS and other prognostic dangerous diagnoses.

Almost in all patients with CBIS, i.e. in adults (1849/2340 or 79%) and in most children (in school age - in 592/870 or 68%, in preschool - in 428/750 or 57%, in children of the first 3 years of life - in 189/540 or 35%), under the eyes appeared intoxication shadows - dark circles with different radii from small to almost, as the patients themselves said, half a face, different color intensity, in almost half of cases - with additional swelling and edema under the eyes. At the same time answering on the doctor's question, when they were first noticed, the answer was approximately the same in most patients: either "from childhood" or "it is hereditary: my mother (or my father) has it". Sometimes pastosity and swelling under the eyes in patients with CBIS were so obvious that they forced patients even to consult a cosmetologist. Here is what a 33-years-old woman, who was diagnosed in our clinic with CBIS on the background of nephrodisbacteriosis with the development of chronic pyelonephritis, told about her meeting with such a "specialist": "The doctor examined me and said that I have "hernias under the eyes", which must be removed by plastic surgery.

One of the typical external manifestations of intoxication effect on the organism of patients with CBIS was amimia, which was more often indicated in adults (1427/2340 or 61%) and school-age children (279/870 or 32%) and much less often in children over 3 up to 7 years (38/750 or 5%). Formerly cheerful, friendly, always with a smile and a play of different emotions on their faces, people seemed to wear either a mournful, or indifferent, or tragic (as in Pierrot from the tale of Pinocchio) mask. The face constantly remained motionless and no longer reflected any emotions

or feelings. It might seem that such a person is not interested in everything that happens around. A great effort had to made the doctor during a long conversation with a such patient, who had already lost faith in doctors and medicine in general, to cause at least some change in facial expression and even a small smile. Here is how one of our patients, a public figure who had been suffering from CBIS for almost 3 long years, commented on what happened to his face before and after treatment: “Doctor, I have almost never smiled in the last year of my illness, I was so sick , so I was exhausted. Although before my smile was my business card, by which I was recognized. Thank you for giving me backs not only a smile, but also my real life".

In this state of severe intoxication more than half of adult patients (1217/2340 or 52.0%) began to lose weight rapidly and body weight could decrease in a short time for 3-6 months from 4-5 kg to, sometimes, 15-20 kg. It is clear that when such rapid weight loss was combined with sub febrile or, moreover, febrile fever and general exhaustion, it did not inspire patients and appeared various phobias, especially locally undetectable cancer and fear of death. This was only exacerbated by the absence of any more or less clear diagnosis that would explain to the person the origin and causes of his terrible physical and mental state.

It should be separately noted that almost 90% (2105/2340) of adult patients with CBIS who had both dominated clinical manifestations of toxins of general toxic action and toxins of other directions, did not have a definite diagnosis for a long time. They were successively treated from Epstein-Barr virus, toxoplasmosis, worms, vitamin deficiency, fulfilled immunomodulation and immuno correction etc., but all in vain - the sick remained ill. These patients with CBIS resembled a neglected child with seven nannies (the child without an eye): each specialist treated his diagnosis symptomatically, but the general state of the patient, unfortunately, did not almost improve after that. Many patients devoted years of their lives and spent their last efforts, which were already scarce, in search of their correct diagnosis and their doctor. As one of our patients (Sasha, 33) said: "Doctor, everybody tired with my complaints and during two years in search of a diagnosis I visited almost all doctors in Kyiv, many - several times", then thought for a moment and sadly added: "No, I must have been wrong: I haven't been to a pathologist yet". Such bitter humor.

Patients with CBIS, unfortunately, usually find themselves in a triple impasse: first in the diagnostic – there is no the correct diagnosis, then in the therapeutic - treatment does not help, and then in life - I am young, beautiful, successful and I’m dying of some unknown disease that absorbs me and no one can help me. Such a bitter truth. But everyone is looking for a way out of this impasse. Some actively and persistently begin to go to different doctors in search of a diagnosis, some itself make this diagnosis and "prescribe" treatment. And someone, unable to do anything, seems to freeze, doing nothing, humbly waiting for a negative "finale". Here is how one mother retold the answer of a doctor who tried to "calm" a dejected woman after her remarks about the very bad and difficult state of her only son: "Don't worry, woman, if it was something serious, your son would have died a long time ago". Yes, usually some does not die from it, but these daily torments cannot be called life. Because toxins in CBIS poison not only the human body but also life itself.

The implications/Conclusions

1. On the basis of clinical observation and laboratory examination in 2009-2020 of 4500 sick children (2160 or 48%) and adults (2340 or 52%) there was formulated and fulfilled the clinical and terminological interpretation of such nosologically separate diagnoses and pathological states as the chronic bacterial intoxication syndrome (CBIS), nephrodisbacteriosis, febrile attack and pain attack.

2. With a pre-established diagnosis of chronic fatigue syndrome to the clinic came almost a third of adults and after examination at the clinic the diagnosis was changed them to CBIS. Among 2340 adult patients with CBIS there were defined in all 100% cases in various combinations at least 4 main clinical symptoms necessary for the diagnosis of CFS, 5 - in 2153 (92%), 6 - in 1849 (79%), 7 - in 1732 (74%) and all 8 - in 1240 (53%). This could most likely indicate that under normal circumstances all these patients should be diagnosed with a previously known CFS with unknown origin etiology.

3. Clinical manifestations of bacterial toxins effect (chronic foci formed in the kidneys) on the human organism in cases of CBIS were conditionally divided into the following groups of symptoms, syndromes and pathological states, clinically combined by lesions of separate organs and systems: generally toxic and mainly neurotropic, including peripheral neuropathies (sensory, motor, autonomic and vasotropic, autonomous), some others and neuralgic, separately - psychotropic, dermatotropic, arthromyotropic and ophthalmotropic.

4. Taking into account the above mentioned direction of toxins in CBIS and the development of relevant clinical symptoms, syndromes and pathological states, which were numbered in total more than 70, they were combined into separate groups and it was created a general summary table of clinical manifestations of CBIS in adults (2340/4500 or 52%) and children (2160/4500 or 48%), including children under the age of 3 years (540/2160 or 25%), from 3 to 7 years (750/2160 or 34.7%) and from 7 to 14 years (870/2160 or 40.3%), as well as there were provided clinical manifestations of toxins of generally toxic action, which caused the most typical symptoms of this disease.

Report 3: Clinical Diagnosis

Abstract

Objective: Of the research was to continue the study of clinical manifestations of CBIS, namely caused by the action of neurotropic toxins.

Design: of the research was clinical-diagnostic and included the determination of clinical manifestations of such a previously unknown disease, which was called chronic bacterial intoxication syndrome (CBIS), which has long been under the guise of a diagnosis of ME/CFS. The studies were prospective-retrospective and were longitudinal. The effectiveness of the obtained results of the study had direct character, because they undoubtedly led to the improvement of the patient's state and life. The style of presentation of the material is narrative, not tedious.

Conditions: The researches were multicenter and conducted in ambulant conditions on the basis of 2 clinics specialized in the field of chronic infectious diseases with a full range of laboratory studies.

Participants: All patients who seeked advice in clinics during 2009-2020 with complaints consistent with a diagnosis of CFS, which was previously diagnosed in almost a third of patients on former stages of examination and treatment.

Results: Report 3 continued to consider the clinical manifestations of CBIS in 4500 children and adults according to Table 1 in Report 2, namely clinical symptoms and pathological states caused by neurotropic toxins. Clinical manifestations of neurotropic toxins included peripheral neuropathies: sensory-motor (paresthesias in fingers, palms, toes, feet, loss of balance and coordination of movements, complications when driving a car (almost 15%) and when walking, muscle weakness and local muscle cramps and twitching by type of muscle fibrillation and fasciculations), autonomic and vasotropic, which were observed in the vast majority of adults (from 65% to 94%) and often (from 5-7% to 54%) in school children age (vegetative-vascular dystonia, orthostatic instability, changes in heart rhythm - tachycardia or bradycardia, pallor, persistent dermographism, sometimes - sluggish pupillary reactions, respiratory disorders - shortness of breathing, feeling of obstruction and spasm in the breath airways, tremor, increased heart rate, changes in blood pressure, "hot flashes" and a feeling of heat, freezing of the extremities, acute spasm of cerebral vessels with temporary transient cerebrovascular accident, sympathoadrenal crises, changes in sweating with the development of increased sweating in more than 3/4 of adults - in 1825/2340 or 78% and almost half of children), as well as autonomous disorders (disorders of internal organs and glands functioning, namely digestion - nausea, vomiting, bloating after eating, constipation or diarrhea, work of the urinary system with urinary incontinence, blurred vision with decreased acuity and visual acuity on which complained 211/2340 or 9% of adults and 35/870 or 4% of school-age children and sexual disorders, including erectile dysfunction, ejaculation problems, decreased libido and potency, which were noted by almost a quarter of men with CBIS - 296/1287 or 23%) and some other neurotropic manifestations of endotoxicosis, such as tics, arachnoiditis, optic nerve neuritis and epileptic seizures. For patients with CBIS due to the action of neurotropic toxins there were very characteristic neuralgia with pain or algic syndrome, which with various clinical manifestations was noted by almost 80% of patients, sometimes with the development of pain attack, with symptoms of trigeminitis (16/2340 adults or 0.7%), occipital nerve neuralgia (9/2340 or 0.4%), external femoral cutaneous nerve (12/2340 or 0.5%), intercostal neuralgia (24/2340 or 1.0%), abdominal pain by type of solaritis (7/2340 or 0.3% in adults and 3/870 or 0.34% in school-age children) or chronic pelvic pain (28/2340 or 1.2%).

The known: existence of a diagnosis ME/CFS with an unknown etiological cause.

The new: for the first time it's clinically determined and laboratory confirmed that under the mask of ME/CFS is hidden still unknown chronic bacterial intoxication syndrome (CBIS), which develops as inflammation of chronic usually locally asymptomatic bacterial infection in kidneys, called nephrodisbacteriosis. For the first time it's determined clinical manifestations of CBIS caused by the action of neurotropic toxins and there was given a clinical description of a pathological state called a pain attack.

The implications/Conclusions: clinical action of neurotropic toxins in CBIS leads to a wide range of symptoms and pathological states, namely peripheral neuropathies (sensory, motor, autonomic and vasotropic, as well as autonomous, including disorders of sexual sphere), some other neurotropic manifestations of endotoxicosis such as tics, arachnoiditis (chronic leptomeningitis), optic nerve neuritis and epileptic seizures, as well as a large list of neuralgias with the pain or algic syndrome, inherent for CBIS, and with the development in some cases of a state called a pain attack.

Key words: chronic bacterial intoxication syndrome (CBIS), nephrodisbacteriosis, neurotropic toxins, neuralgia, pain attack, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

In previous Report 2 there were considered the clinical manifestations of CBIS caused by toxins of general toxic action. The Table 1 in Report 2 shows that clinical symptoms and pathological states caused by neurotropic toxins were next in emergence frequency. Clinical manifestations of neurotropic toxins included peripheral neuropathies (sensory, motor, autonomic and vasotropic, as well as autonomous) and some other neurotropic manifestations of endotoxicosis, such as tics, arachnoiditis, optic nerve neuritis and epileptic seizures, as well as a large list of neuralgias.

Neuropathy is usually considered as a disease or dysfunction of nerves function or a single nerve. It is known that any nerve fibers in all parts of the body can be damaged due to injury, illness or due to the action of exogenous toxins and poisons, i.e. toxic neuropathies. In the case of nephrodisbacteriosis and the development of CBIS a special type of endotoxic neuropathy develops, which from a clinical point of view was considered as a pathological state that emerged due to the neurotropic action of bacterial toxins.

Neuropathy is classified according to the type and location of the nerve damage. Peripheral neuropathy is a general term used to describe changes that occur when peripheral nerves are affected, which include all nerves outside the brain and spinal cord. Taking into account the existence of 3 types of peripheral nerves (sensory, motor and autonomic), the corresponding types of neuropathies were distinguished. Sensory-motor include such changes in sensations in the fingers, palms, toes, feet as numbness, "creeping ants", loss of sensitivity or, conversely, increased sensation of cold, tingling or pain, sometimes pronounced, burning, spreading along the leg towards the body, itching or heartburn. Such paresthesias and other manifestations of peripheral limb neuropathies were observed in 2/3 of adults (1568/2340 or 67%), and even in 7% of school-age children (61/870). Sometimes there was an inability to determine the position of the extremities in the samples of Bar, Rusetsky, Buddha due to bathianesthesia, i.e. loss of vibration sensitivity in the extremities. In such patients there was emerged sensitive ataxia that led to incoordination of movements, swaying when walking and frequent falls, especially at dusk with limited visual function. A striking example of sensory polyneuropathy was hypersensitivity of the skin to touch that indicated an increased threshold of pain sensitivity and its distortion (hyperesthesia, hyperalgesia, dysesthesia etc.).

When the motor nerves are damaged, there were occurred motor neuropathies. Patients with CBIS, mostly adults (421/2340 or 18%) complained of periodic loss of balance and coordination, which could complicate walking, especially descending stairs, getting off the subway escalator, getting out

of the car etc., which were complained of 12% of adults (281/2340) and only sometimes (18/870 or 2%) schoolchildren. Almost 15% of patients, among those who drove a car (77/515), noted violations and even sometimes loss of habitual skills and coordination of movements, which made driving difficult and sometimes forced them to give up driving for a certain period. Some patients with CBIS noted some difficulty when performing actions with small objects (such as a pen, pencil or shirt buttons). With predominant motor nerve damage, patients complained of muscle weakness (211/2340 or 9% adults and 18/870 or 2% of schoolchildren), there were sometimes occurred local convulsions and twitching more often in the extremities of the type of muscle fibrillation and fasciculations (328/2340 or 14% of adults and 35/870 or 4% of schoolchildren). The direct speech of a young athletic guy who trained in the gym every day: "I can't keep my head straight now for a long time, my neck muscles have become a bit weak."

Peripheral autonomic neuropathies often with symptoms of predominantly vascular origin were considered as a clinical manifestation of neurotropic or perhaps more precisely neurovasotropic toxins and were observed in the vast majority of adults (65% to 94%) and often in school-age children (5-7% to 54%). Symptoms of vegetative-vascular dystonia (VVD) were present in 94% (2200/2340) of adult patients with CBIS and 23% (200/870) of schoolchildren. The development of symptoms, as a rule, was due to the long-term pathological effect of endotoxins on the vascular-nervous bundles with a violation of the conduction of nerve impulses in the walls of blood vessels and directly in the tissues. Under VVD there was understood a functional disorder or dysfunction of the autonomic nervous system that is characterized by a violation of the general state and well-being and is felt as a failure of functioning various organs and systems.

Taking into account the universal character of the functional presence of the autonomic nervous system in almost all organs and systems, the symptoms of VVD had variegated character and seemed to be "scattered" throughout the whole organism. In case of VVD and peripheral autonomic neuropathies, there were observed such symptoms as orthostatic instability with mild dizziness (in 1802/2340 or 77% of adults and 270/870 or 31% of school-age children) in some cases until orthostatic collapses with loss of consciousness but without convulsions and involuntary urination. In 1755/2340 or 75% of adults and 157/870 or 18% of schoolchildren there were observed changes in heart rhythm (tachycardia or bradycardia), pallor, persistent dermographism, sometimes - sluggish pupillary reactions, respiratory disorders (shortness of breath, feeling of obstruction and spasm in the respiratory tract), tremor. Increased heart rate was experienced by the vast majority of adults (1638/2340 or 70%) and very rarely - schoolchildren (only 122/870 or 14%), blood pressure drops - respectively 1521/2340 or 65% adults and 61/870 or 7% schoolchildren, "hot flashes" and a feeling of heat - more than 2/3 of adults (1638/2340 or 70%). Due to spasm of peripheral vessels, every 4 of 5 adult patients with CBIS (1895/2340 or 81%) experienced freezing of the extremities, but school-age children (44/870 or 5%) almost ignored this complaint.

At the same time it appeared that in case of CBIS it is possible development of not only chronic spasm and not only peripheral vessels. In 70/2340 (3%) adults due to acute cerebrovascular spasm

it was registered (often in the recent anamnesis and sometimes - during the examination in the clinic before treatment) temporary transient cerebrovascular accident with a typical focal, generally cerebral or mixed symptomatics with complete recovery of neurological symptomatics within a few hours. In 280/2340 (12%) adults with autonomic neuropathies there was a rapid development of sympathoadrenal crises, which were usually unpredictable and began with a sudden headache, palpitations, paleness or on the contrary redness of the face, which were often accompanied by chills, tremors and numbness of the extremities, usually with sharply expressed uncontrollable anxiety and the subsequent development of a panic attack. In some cases CBIS could acutely debut just from the sympathoadrenal crisis with the subsequent development of more typical symptoms of this disease.

It should be separately emphasized that the frequent use of the terms "vegetative-vascular dystonia" and similar in meaning "neurocirculatory dystonia" occurs because of that such syndromic diagnoses are convenient because they allow not to waste time on the diagnostic search for specific causes of the disorder. Making such diagnoses usually leads to inappropriate and ineffective treatment of the basic disease, which remains undefined, which for many years worsens the disease prognosis and quality of patients' life.

Taking into account the high frequency of autonomic disorders in case of CBIS, one can assume that in the absence of a clear relationship between VVD with such primary diseases as mental disorders, certain somatic diseases, organic lesions of the CNS, hypertension, endocrine disorders, chronic coronary heart disease and so on, it makes sense to examine bacteriologically the urine of patients with an etiologically uncertain diagnosis of VVD for presence nephrodisbacteriosis and CBIS. Moreover that the reports about presence at VVD such symptoms as quick fatigue, joint pain, sleep disturbances, prolonged slight temperature increase, chills or fever, as well as difficult, rare or frequent urination is too reminiscent the clinical manifestations of just CBIS.

Peripheral autonomic neuropathies also included changes in sweating due to dysfunction of the sweat glands with excessive or on the contrary insufficient sweating, which very often for some time could become the main complaint of the patient. More than 3/4 of adults (1825/2340 or 78%) had changed character of sweating due to the general intoxication: usually daytime sweating more often increased, which was not preceded by exercise or agitation. Sweating could be from moderate to profuse, sometimes with a sharp unpleasant odor of sweat, which could not be washed (direct speech: "I take a shower 5 times a day and still feel the stench"), less often - on the contrary with almost no sweating and constant dryness of the skin and even mucous membranes (mouth, eyes, vagina).

Increased sweating was a typical manifestation of CBIS in almost half of infants and the first 3 years of life (260/540 or 48%), preschool age (278/750 or 37%) and schoolchildren (470/870 or 54%). In young children increased night sweating was more often observed, especially when falling asleep, when often the T-shirt and pillowcase, and sometimes even the pillow became so wet with sweat that, according to mothers, "they could be twisted" and had to be changed several times a night. In the case of the smell of sweat in children of early school age (8-12 years) with CBIS, their parents

and doctors mistakenly regarded it as a manifestation of "early puberty". At the same time such false conclusions could be applied not only to boys but also to girls.

Sweat glands dysfunction, which causes either excessive or insufficient sweating, which was considered as a typical manifestation of peripheral autonomic neuropathies, is sometimes referred to as autonomous neuropathy. Autonomous neuropathy-based on damage of nerve fibers responsible for the functioning of internal organs and glands, namely: the heart, blood circulation (including blood pressure), digestion, bladder function and intestinal motility, sexual function, sweating - can manifest itself with various symptoms. Some of them we observed in patients with CBIS (see Table 1). Almost 19% of adults (444/2340) complained of nausea, which could occur before breakfast and sometimes even lead to vomiting, constant bloating after each meal, which hardly responded to symptomatical treatment with enzymes, cholagogues, sorbents and probiotics and constantly occurred again and again. Because they were not connected with dysfunction of the gastrointestinal tract, but with the suppression of vagus nerve function. Similar symptoms were also noted by 14% (122/870) of schoolchildren and 11% (83/750) of preschool children. Digestive difficulties, connected with autonomic neuropathy, have also caused digestive function disorders and slowed gastric emptying (gastroparesis). Due to that there were such phenomena as a feeling of over-satiety after eating a small amount of food, loss of appetite with possible subsequent weight loss, difficult swallowing and heartburn. Adults (258/2340 or 11%) and school-age children (87/870 or 10%) complained of constipation or diarrhea almost equally often. In this case the problems of bowel movements could both coincide with bloating and be observed separately from it. The frequency of these symptoms in preschool children, which could be clearly associated with CBIS, remains uncertain.

Quite often (in almost a third of cases: in 680/2340 or 29% of adults, in 218/870 or 25% of school-age children, in 240/750 or 32% of preschool children and in 49/540 or 9% of children under the age of 3 years) were noted disorders of the urinary system: accelerated or rare (2-3 times a day) urination, difficulty in starting urination, partial urinary incontinence, especially during physical and emotional loading and during sneezing, coughing, laughing etc., a feeling of incomplete emptying of the bladder. However symptoms and laboratory signs of cystitis emergence or sharpening could usually be absent.

Almost a quarter of men with CBIS (296/1287 or 23%), usually young and sexually active between the 30 and 50 years-ages, noted such features of autonomous (autonomic) neuropathy as sexual dysfunction, including an inability to achieve and maintain an erection (erectile dysfunction), problems with ejaculation, decreased libido and potency. It is known from the literature that autonomic neuropathies of the genitals can lead to sexual dysfunction not only in men, but also cause vaginal dryness (on which, among other things, repeatedly complained women with CBIS and urogenital dysbacteriosis) and difficulties with orgasm in women. Although this "women's" question at CBIS requires a separate professional study and observation. However it can already be noted that after the start of treatment of nephrodisbacteriosis and CBIS, sexual function in almost

all men was partially or completely restored. That is it can be stated that bacterial vaccines, as it was previously accidentally found in today's most common means to increase sexual function, and initially a purely cardiac drug, also have a "side effect": the restoration and enhancement of sexual success. Here is what happened to one of our patients and how he talked about his feelings.

Example 1

A 47-years-old man went to the clinic in 2016 for gouty poliarthritis, which was almost impossible to calm down during the previous years of continuous treatment after diagnosis gout. He has been living outside Ukraine for a long time in one of the most developed countries in Europe. For almost 5 years he was on allopurinol therapy and was constantly receiving NSAIDs, periodically up to 3-4 times a year were prescribed antibiotics. The condition did not improve, the inflammation of the joints lasted and was asymmetrical with a violation of the configuration, the pain sometimes became unbearable. The patient noted that on the eve of the next attack of arthritis, the body temperature rose sharply to 38-39°C, felt chills, loss of strength, headache and other symptoms of general intoxication. The level of uric acid in the blood very often did not correlate with the appearance and intensity of joint pain: at high levels it could be completely absent, and at below the threshold - unbearably strong. Additionally he noted general weakness, increased fatigue, memory impairment, logical thinking, decreased vital energy and work efficiency, the last 3-4 years - erectile dysfunction with a significant deterioration in libido and potency. From the anamnesis it was known about the presence of chronic prostatitis in the stage of stable remission, which was also repeatedly treated with antibiotics, periodically experienced dysuric symptoms with accelerated urination.

Due to the lack of a positive clinical effect from the therapy, and taking into account the detection of HLA-B27 antigen in molecular-genetic testing, it was decided by the place of previous treatment to prescribe him cytostatic therapy, which he was very scared. He flew to Kyiv and consulted the Vitacell Clinic. It was established a preliminary diagnosis of nephrodisbacteriosis with the development of CBIS and dominant reactive polyarthritis on the background of gout, which was not significant in the development of arthritis. The diagnosis was confirmed by bacteriological examination of warm urine with the detection of 3 urine cultures of Enterococcus faecalis and 3 - *E. coli*. Already during the first course of treatment with divalent Escherichia coli-Enterococcal bacterial autovaccine with 10 injections the joint pain significantly reduced, normalized their configuration, the patient stopped taking allopurinol and reduced the dose of nonsteroidal anti-inflammatory drugs. After finishing of the second course of treatment with the bacterial autovaccine (also with 10 injections), he completely stopped taking anti-inflammatory drugs and for the next 4 years did not take more NSAIDs and allopurinol.

During the first 5-6 months after the start of treatment with bacterial autovaccines, the general state significantly improved: weakness and increased fatigue passed, impaired memory and logical thinking were restored, vital energy and work efficiency returned. In five months after starting treatment at the clinic, the patient humorously "complained" that he had not been warned about the

presence of "side effects" in bacterial vaccines: they had improved so much his libido and potency that were almost lost during the previous treatment period that “his wife began to hide”.

During the observation period in the clinic (according to the results of control bacteriological cultures of warm urine after previous courses of treatment) he took 4 cycles of vaccination per 2-3 courses each. Periodically he notes still episodes of short-term fever (febrile attacks connected with nephrodisbacteriosis) with the appearance of minor joint pain, which disappears on its own in 1-2 days. Periodic bacteriological examinations of warm urine are continued. In September 2020 despite the absence of clinical complaints and due to the release of new urine cultures during the control bacteriological examination, at the request of the patient he was prescribed the next preventive 5th cycle of treatment with two bacterial autovaccines. He has no longer problems with joints and sexual function.

Another clinical variant of autonomous neuropathy was blurred vision with decreased visual acuity and clarity, which was complained of by 211/2340 (9%) adults and 35/870 (4%) school-age children. Image blurring was temporary, usually with other manifestations of CBIS, although it could recur unpredictably over several years. It can be assumed that such visual disturbances were connected not only with autonomic neuropathy, but also with retinal vasospasm. Moreover, when examining the fundus by an ophthalmologist it was usually nothing found in these cases but a slight spasm of retinal vessels.

Symptoms of peripheral neuropathy in CBIS developed more often slowly, but sometimes could occur suddenly. They manifested to a greater or lesser extent at a certain time depending on the level of intoxication and correlated with the general state of the patient during treatment.

Some other manifestations of neurotropic toxins action include tics, arachnoiditis and epileptic seizures. Tics was considered to be rapid involuntary muscle movements of the same type, which could sometimes affect the vocal apparatus, accompanied by vocalization (proclamation of various sounds), respiratory muscles (grunting, coughing, whistling or wheezing, loud exhalation or inhalation). Tics were more often observed in schoolchildren (148/870 or 17%) than in preschool children (53/750 or 7%) and adults (79/2340 or 3%). More often tics were long-lasting (more than 1 year), had local character with the involvement of one group of muscles (facial expressions, most often - blinking) and simple with elementary movements (squinting, winking, ear movements, frowning, raising eyebrows). But in some cases they were complex and generalized involving several muscle groups, reminiscent of purposeful motor act, as in the following observation.

Example 2

The clinic was attended by the parents of a 10-years-old boy, a fourth-pupil, who had been called to school several times before because of "bad behavior" of their son. In the middle of the lesson the boy stood up from the desk, made a full 360° rotation around himself, saying something like a grunt, and sat down again. There were no other remarks on the behavior of a pupil who was polite and studied well. Neither long explanatory conversations, no bad marks in the diary, no threats

from parents to refuse to walk, ride a bike etc. had no positive effect: the boy continued to "wind" his revolutions. During the consultation at the clinic he was diagnosed with nephrodisbacteriosis with CBIS (from the anamnesis were established episodes of cystitis in preschool age), which along with other generally toxic symptoms dominated by the manifestations of neurotropic toxins action in the form of complex generalized tics. The child's state corresponded to the classic clinical manifestations of Gilles De La Tourette's syndrome (or simply - Tourette's syndrome), which is manifested by motor and vocal tics with coprolalia. In this case coprolalia is considered the most severe manifestation of the syndrome and one of the diagnostic criteria of the disease. The diagnosis of nephrodisbacteriosis was confirmed by isolation of 3 urine cultures of Enterococcus faecalis. Immediately after the first course of treatment with bacterial enterococcal autovaccine "jumps" almost stopped and "hooligan" again became an excellent pupil.

The next clinical diagnosis connected with the action of neurotropic toxins was considered to be the onset of symptoms of arachnoiditis, which were observed in 374/2340 or 14% of adults. Arachnoiditis or serous inflammation of the arachnoid membrane of the brain or spinal cord has usually infectious origin, namely - more often develops due to herpes viruses. Although from an anatomical point of view, given the lack of microvessels in the arachnoid membranes, and there cannot be the inflammatory process in them, and they cannot cause headaches. Moreover, in modern medicine the term "arachnoiditis" in general remains controversial and is not recognized by all experts: instead of arachnoiditis now is used more often the term chronic leptomeningitis. Therefore there is not the isolated lesion of the arachnoid membrane of the brain in arachnoiditis due to the lack in its own vascular system, and the infection in arachnoiditis usually passes from the soft meninge.

Careful PCR-examination of these patients for all herpes viruses did not confirm their etiological role in the emergence of arachnoiditis. Moreover, almost half of patients (182/374 or 48.7%) in the previous stages of treatment in other medical institutions have already received antiviral drugs with temporary or no positive clinical effect. In all patients in this group there was detected a focus of nephrodisbacteriosis in the kidneys, usually locally asymptomatic, and other symptoms of CBIS. Taking into consideration that in many cases the cause of arachnoiditis remains unclear, there was considered the occurrence in patients with CBIS of one of the main symptoms, headache, as a manifestation of endotoxic irritation of the soft meninges. Herewith there are usually disorders of cerebrospinal fluid circulation and venous congestions, which lead to increased intracranial hypertension, frequent and prolonged cephalgia.

Moreover besides headache, such well-known general cerebral symptoms in patients with a diagnosis arachnoiditis (and in fact - chronic leptomeningitis) as dizziness, sometimes - with loss of consciousness (collapse), tinnitus (sometimes with painful sensitivity to sounds of type hyperacusis), eyes movement disorders sometimes with the appearance of horizontal nystagmus, decreased vision, loss of visual fields, as well as memory impairment, irritability, general weakness and fatigue, sleep disturbances – were very similar to the general toxic symptoms of CBIS. After treatment with bacterial autovaccines most of these symptoms, either arachnoiditis or CBIS,

weakened and more often completely disappeared.

Probably the following may seem unbelievable to some experts, but neurotropic toxins proved capable to cause epileptic seizures. At the beginning so surprised also we considered these previously unknown clinical cases, which seemed completely exceptional, the first of which was registered in October 2008 [1].

Example 3

For the first time the mother of the girl Olenka, 10 years old, went to the clinic on October 28, 2008. She left the child at home (in another city of Ukraine), came to Kyiv alone because she was afraid of new epileptic seizures and probably did not know if she selected the correct address. A conversation with an almost desperate woman revealed the following. The first epileptic seizure occurred at the age of 5 years after a sharp rise of temperature and resembled febrile seizures, which often occur in children during high fever and usually disappear quickly forever. But not in this child. All subsequent attacks repeatedly 1-2 times a month, occurred just on the background of a sudden rise of temperature that occurred almost constantly. Due to the lack of foci of bioelectric activity in the brain on the EEG, the etiology of the attacks remained unclear. But it was clearly recorded that during the rise of temperature and epileptic seizures in the urine was always an increased content of leukocytes and protein, although no one paid much attention to it. From an in-depth anamnesis, during a conversation with Olenka's mother, it was additionally established that beginning from the age of 3 the child periodically for no apparent reason and without catarrhal phenomena suddenly had a fever of up to 39°C which lasting several hours or days, disappeared. That is long before the onset of epileptic seizures there were typical febrile attacks which are the hallmark of nephrodisbacteriosis and CBIS. Each time this state was regarded and treated as "SARS" and almost every time antibiotics were prescribed. And only in January 2008 after urgent hospitalization in the nephrology department, when the temperature once again rose to 40°C, and in the analysis of urine leukocytes already covered all fields of vision, there was for the first time established the diagnosis of acute pyelonephritis and there was first isolated pure culture *E.coli* from urine. During the conversation the girl's mother noted that additionally to the temperature the child complained of constant and sometimes severe headache, weakness, quick fatigue, periodical joint pain. The child also had a constant low-grade fever, increased sweating, as well as decreased concentration and memory impairment, which were mistakenly associated with epilepsy. That is there were typical, as for a child, manifestations of CBIS. During the examination of the child in the clinic there was isolated from the urine a large amount of *E.coli* (twice) and Enterobacter aerogenes. A divalent autovaccine was prepared from the isolated bacteria and immunization of the child was started on December 4, 2008. After almost every injection the temperature rose to 38-39°C that was considered as a sign of mass death of bacteria in the kidneys under the influence of own immune system with the release of toxins of general toxic action with a pyrogenic effect. But despite the high temperature convulsions no longer occurred, despite the fact that from the beginning of treatment with the bacterial vaccine the child no longer took anticonvulsants. During the year she received several more courses of vaccination with bacterial autovaccines. According

to the mother (contacted by phone on February 24, 2010), there were no more epileptic seizures and febrile attacks, the subfebrile passed, the joint pain did not bother her, the child became more active, happier and started learning better at school.

Over the next 12 years we observed 120 children (under 3 years of age - 16/540 or 3%, from 3 to 7 years - 60/750 or 8% and schoolchildren - 44/870 or 5%), whom was previously diagnosed (after examinations in other clinics) epileptic syndrome of unknown etiology. A certain frequency of episyndrome of toxic origin in adults remained clearly not established, although a small number of such patients were also under our supervision.

All children with epileptic seizures during the examination and treatment in our clinic continued to be under the supervision of a neurologist at the place of observation. Additionally all children in the clinic were examined by ELISA and PCR for herpes viruses (HSV, EBV, CMV, HHV-6), based on which at the time of admission to our clinic herpetic etiology of episyndrome, which in children is more often connected with fetal cytomegalovirus infection [2], was completely ruled out. Although almost a third of children based on the detection of "high titers" of IgG antibodies have already previously received antiviral treatment, which did not help them. The duration of existence of epileptic syndrome in children was different and ranged from 1-2 years (34/120 or 28.3%) to 3-8 years (86/120 71.7%). In 29/120 cases (24.2%) epileptic seizures were manifested by typical absences with a sudden short-term loss of consciousness. In 97/120 (80.8%) children on the EEG there were detected signs of epileptiform activity of usually diffuse character, but in the other 23/120 (19.2%) - epileptiform discharges were not registered at all. Among 97 children with epileptiform disorders on EEG in 21/97 (21.6%) cases there were no seizures or absences at all. More than half of the children (67/120 or 55.8%) received anticonvulsants with limited clinical efficiency.

Besides epileptic syndrome as a manifestation of neurotropic toxins action, each child also had other symptoms of CBIS. Treatment with bacterial auto vaccines was fulfilled for 102/120 (85%) children, follow-up observation was in 77 cases. The cessation of epileptic seizures simultaneously with disappearance of other manifestations of CBIS was observed in 62/77 (80.5%) cases, herewith seizures often discontinued already after the first course of vaccination. The same positive changes occurred on the EEG: signs of epileptiform activity decreased and gradually completely disappeared, sometimes - even during vaccination.

Diagnostics of cases of epileptic syndromes of endotoxic origin among children with CBIS, the etiology of which remained till the moment being unclear, and the first positive results of their treatment without antibiotics and the gradual reduction and subsequent abolition of anticonvulsants with cessation of seizures and normalization of the EEG, deserve attention. Because it can give these children a chance to get rid of this problem and recover. Although, of course, the question of episyndrome of toxic origin in patients with CBIS on the background of nephrodisbacteriosis and pyelonephritis requires the further study by specialists in this field.

The clinical manifestations of neurotropic toxins also included a large list of neuralgias. Neuralgia

meant damage to peripheral nerves, characterized by attacks of pain in the area of innervation of a certain nerve. In contrast to neuritis, for neuralgia there were no movement disorders and loss of sensitivity, although often it was noted hypo- or hyperesthesia in the area of innervation, pain on palpation, especially nerve exit points. In the affected nerve in such cases, according to the literature, there are no structural changes. It is known that neuralgia can occur in any part of the body, from the head to the soles of the feet. In most cases neuralgia occurs as a result of various injuries, infections, severe colds or hypothermia. At CBIS it is about toxic defeat of peripheral nerves by endotoxins of the bacteria having the chronic inflammation focus in kidneys. Despite the gradual character of the development of nephrodisbacteriosis itself and in contrast to peripheral neuropathies, which more often developed slowly, the appearance of neuralgia had usually paroxysmal character with the development in the shortest time of excruciating pain in various locations. Just for these cases we used the term pain attack with the rapid development in patients with nephrodisbacteriosis and CBIS of pain feelings of various locations of paroxysmal and often intolerable character, usually without the development of inflammatory processes, more often prolonged recurrence. Together with classic neuralgia (such as trigeminitis, solaritis, intercostal neuralgia) pain attacks could be accompanied by attacks of headache, cardialgia, joint and spine pain, muscle pain, pelvic pain etc.

According to the information available for neuralgia, it is known that the most frequent form is trigeminal nerve damage, which we observed in 16/2340 (0.7%) adults with CBIS; less often it is thought about occipital nerve neuralgia, which we observed in 9/2340 or 0.4% of adults, accompanied by so-called "shooting pain in the head" with the spread in some cases of pain in the eyes, temples or forehead. The clinical picture of external thigh cutaneous nerve neuralgia, which was observed in 12/2340 or 0.5% of adults, increased gradually. Usually patients first noticed numbness of certain areas of the skin on the outer thigh, loss of tactile and pain sensitivity, followed by the development of pain syndrome, which often depended on the position of the leg and body. Intercostal neuralgia, which was very similar to shingles but without the typical herpetic rash, was observed in 24/2340 or 1.0% of adults.

It should be noted that the pain or algic syndrome in general was very characteristic for patients, children and adults, with CBIS: in almost 80% of cases in various clinical manifestations of this pathological state the pain was present or dominated in the clinical picture of the disease and included such manifestations as constant or paroxysmal migraine type headache, pain in the scalp of the scalp ("as if the roots of the hair hurt"), sudden paroxysmal sometimes unbearable, shooting, burning pain on the face along the branches of the trigeminal nerve by type of trigeminitis, orbital pain, sore throat, painful on palpation cervical or axillary lymph nodes. 281/2340 or 12% of adults and 9/870 or 1% of schoolchildren had complaints of lung pain during breathing, which could be accompanied by such respiratory disorders as shortness of breathing or a feeling of obstruction and spasm in the breathing tracks.

More than a third of adults (889/2340 or 38%) complained of chest pain, long-term pain and compression in the heart area were noted by more than half of patients with CBIS (1264/2340 or 54%) and even 70/870 (8%) of schoolchildren. Clinically cardialgia and chest pain often could even

imitate a myocardial infarction, therefore in 477/1264 (37.7%) cases there were all clinical reasons to do an ECG, and in some cases of prolonged pain duration for several days and even weeks - even several times. Separately it should be emphasized on the existence of a theoretical possibility of endotoxic myocarditis development. That is not due to exotoxins as in alcohol poisoning, renal failure, heavy metal vapor poisoning, but connected with bacteria toxins, when the inflammatory process in the myocardium occurs on the background of nephrodisbacteriosis/pyelonephritis with the development of severe endotoxicosis and CBIS. It is possible that a significant proportion of endotoxic myocarditis passes under the masks of influenza, herpes, chlamydia, streptococcal and other infectious myocarditis, because it is unlikely that for any of the patients with such diagnoses there was conducted a targeted bacteriological examination of urine. We observed several such patients with CBIS after a recent myocarditis, in which it was possible to assume such a variant of myocardial damage, but the evidence base was not enough and this question requires further study.

The patients with CBIS under our supervision, 1100/2340 (47%) adults, 270/870 (31%) schoolchildren and 113/750 (15%) children aged 3 to 7 years had pain in the joints of varying intensity and duration and sometimes along the tendon. Almost 2/3 of adults (1404/2340 or 60%) and 104/870 (12%) of schoolchildren (more often teenagers) experienced spinal pain (spondylalgia). This pain could not be connected with the existence and exacerbation of chronic osteochondrosis or intervertebral hernia, so far as it could not be alleviated by well-known treatment in such cases. Spinal pain sometimes became so severe and persistent that some patients were even forced to seek the advice of neurosurgeons. In some adults spinal pain had clinical signs of ankylosing spondyloarthritis (Bekhterev's disease). 585/2340 (25%) adults and 44/870 (5%) schoolchildren experienced muscle pain and sometimes muscle stiffness of varying intensity. Sometimes muscle pain and stiffness dominated in the clinical picture of disease by type fibromyalgia syndrome. Algic manifestations from the joints, spine and muscles were attributed to clinical states caused by arthromyotropic toxins action.

The implications/Conclusions

1. To the clinical manifestations of neurotropic toxins belong peripheral neuropathies (sensory, motor, autonomic and vasotropic, as well as autonomous) and some other neurotropic manifestations of endotoxicosis, such as tics, arachnoiditis, optic nerve neuritis and epileptic seizures, as well as a large list of neuralgias. Sensory-motor neuropathies included paresthesias in the fingers, palms, toes, feet, loss of balance and coordination, difficulty of driving (almost 15%) and walking, muscle weakness and local cramps and muscle twitching (by type of muscle fibrillation).

2. Peripheral autonomic neuropathies often with symptoms of predominantly vascular origin were considered as a clinical manifestation of neurotropic or perhaps more precisely neurovasotropic toxins action and it was observed in the vast majority of adults (65% to 94%) and often in schoolchildren (5-7% up to 54%). Symptoms of vegetative-vascular dystonia (VVD) were present in 94% (2200/2340) of adult patients with CBIS and 23% (200/870) of schoolchildren.

3. Simultaneously with VVD there were observed such symptoms of peripheral autonomic

neuropathies as orthostatic instability with mild dizziness (in 1802/2340 or 77% of adults and 270/870 or 31% of schoolchildren) before orthostatic collapses in some cases even with loss of consciousness. In 1755/2340 or 75% of adults and 157/870 or 18% of schoolchildren there were changes in heart rhythm (tachycardia or bradycardia), pallor, persistent dermographism, sometimes - sluggish pupillary reactions, respiratory disorders (shortness of breathing, feeling of obstruction and spasm in the respiratory tract), tremor. The vast majority of adults (1638/2340 or 70%) experienced increased heart rate, blood pressure drops (1521/2340 or 65%), "hot flashes" and a feeling of heat - more than 2/3 of adults (1638/2340 or 70%). Due to the spasm of peripheral vessels every 4 out of 5 adult patients with CBIS (1895/2340 or 81%) experienced freezing of the extremities.

4. In 70/2340 (3%) adults with CBIS due to acute cerebrovascular spasm there was registered a temporary transient cerebrovascular accident with typical focal, general cerebral or mixed symptomatics with its complete reversibility within a few hours. In 280/2340 (12%) adults with autonomic neuropathies there was the development of sympathoadrenal crises, usually with pronounced uncontrollable anxiety and the subsequent development of a panic attack.

5. Peripheral autonomic neuropathies also included changes in sweating due to dysfunction of the sweat glands with usually excessive or sometimes on the contrary insufficient sweating. More than 3/4 of adults (1825/2340 or 78%) had increased sweating on the background of general intoxication, which was not preceded by physical exertion or arousal. Sweating could be from moderate to profuse, sometimes with a sharp smell of sweat, less often - on the contrary with almost complete absence of sweating and constant dryness of the skin and even mucous membranes (vagina, mouth, eyes). Increased sweating was a typical manifestation of CBIS in almost half of infants and the first 3 years of life (260/540 or 48%), preschool age (278/750 or 37%) and schoolchildren (470/870 or 54%).

6. In CBIS-patients with autonomic neuropathies there were separately singled out autonomic neuropathies which included functional disorders of the internal organs and glands, namely: digestion (nausea, vomiting, bloating after eating, constipation or diarrhea), which were badly healed by normal in such cases symptomatic treatment and which were observed in 19% of adults and 10-14% of children, functioning of the urinary system with urinary disorders, partial urinary incontinence etc., which bothered 29% of adults and 9-25% of children in different age groups, as well as blurred vision with decreased visual acuity and clarity, which was complained of by 211/2340 (9%) adults and 35/870 (4%) schoolchildren.

7. Almost a quarter of men with CBIS (296/1287 or 23%), usually young and sexually active age from 30 to 50 years, noted such manifestations of autonomous (autonomic) neuropathy as sexual disorders, including the inability to achieve and maintain an erection (erectile dysfunction), problems with ejaculation, decreased libido and potency. After starting treatment of nephrodisbacteriosis and CBIS with bacterial vaccines, sexual function in almost all men was partially or more often completely restored.

8. Some other manifestations of neurotropic toxins action during CBIS were tics, which were observed in 7% of children aged 3 to 7 years and in 17% of schoolchildren, arachnoiditis (in 16% of adults) and epileptic seizures, which occurred in 3% of children under 3 years, in 8% - from 3 to 7 years and in 5% of schoolchildren.

9. It was found that for patients with CBIS due to the action of neurotropic toxins there was very characteristic the pain or algic syndrome: in almost 80% of cases in various clinical manifestations of this pathological state the pain was present or even dominated in the clinical picture of the disease sometimes with the development in shortest time of intolerable pain of different location by type of pain attack and included symptoms of: trigeminitis (in 16/2340 adults or 0.7%), occipital nerve neuralgia (9/2340 or 0.4%), external cutaneous nerve of the thigh (12/2340 or 0.5%), intercostal neuralgia (24/2340 or 1.0%), abdominal pain by type of solaritis (7/2340 or 0.3% in adults and 3/870 or 0.34% in schoolchildren) or chronic pelvic pain (28/2340 or 1.2%), chest pain (889/2340 or 38%) and in the heart area (in 1264/2340 or 54% of adults and in 70/870 or 8% of schoolchildren), lung pain when breathing (in 281/2340 or 12% of adults and 9/870 or 1% of schoolchildren), and a headache sometimes of the type of migraine, pain in joints, in spine, in muscle, in eyes orbits, sore throat, painful on palpation cervical or axillary lymph nodes etc.

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Report 4: Clinical Diagnosis

Abstract

Objective: of the research was to continue the study of clinical manifestations of CBIS, caused by neurotropic toxins action (namely algic states), as well as psychotropic and dermatotropic toxins.

Design: Of the research was as previously clinical-diagnostic and included the determination of clinical manifestations of such a still unknown disease, which was called chronic bacterial intoxication syndrome (CBIS), which has long been under the mask of a diagnosis of ME/CFS. The studies were prospective-retrospective and were longitudinal. The effectiveness of the obtained results of the study had direct character, because they undoubtedly led to the improvement of the patient's state and life.

The style of presentation of the material is narrative, not tedious.

Conditions: The researches were multicenter and conducted in ambulant conditions on the basis of 2 clinics specialized in the field of chronic infectious diseases with a full range of laboratory studies.

Participants: All patients who seeked advice in clinics during 2009-2020 with complaints consistent with a diagnosis of CFS, which was previously diagnosed in almost a third of patients on former stages of examination and treatment.

Results: There were detailed studied such states important in the diagnosis plan and treatment that occur in patients with CBIS under the influence of neurotropic toxins, such as trigeminal neuralgia, abdominal pain by the type of solaritis, chronic pelvic pain or fibromyalgia or fibromyalgic syndrome. Clinical manifestations of psychotropic toxins in patients with CBIS included severe asthenic syndrome, rapid exhaustion, various cognitive impairments with memory impairment, logical and associative thinking, decreased concentration, attention, reduced mental abilities, reduced vital motivations and interest to surroundings, social dis adaptation, phobias with subsequent development of panic attacks in 74% of adults and 9% of schoolchildren, fear of death or vice versa - unwillingness to continue such a painful life: 28% of adults and even 1.4% of schoolchildren had suicidal thoughts. In 12/2340 (0.5%) adults with typical clinical manifestations of CBIS there was observed the onset of depersonalization/derealization syndrome, in 19/2340 (0.8%) adults - manifestations of manic-depressive syndrome. Clinical manifestations of dermatotropic toxins included itching of the skin and mucous membranes (44% of adults and 17% of schoolchildren), brittleness and damage to the nails (39% and 1.3% respectively), constant or paroxysmal burning and a feeling of "sand" in eyes, which caused moderate or insurmountable tearing (57% and 8% respectively), a feeling of obstruction in the throat (52% and 2.7% respectively), prolonged reflex cough, which was noted by 29% of adults, 25% of schoolchildren, 19% children aged 3 to 7 years and 7% of infants and under 3 years of age with the possible development of pertussis syndrome, increased hair loss (53% of adults and even 3% of schoolchildren) and alopecia, which were noted by 92/2340 (3.9%) adults, among them women significantly prevailed (68/92 or 73.9%).

The known: existence of a diagnosis ME/CFS with an unknown etiological cause.

The new: for the first time it's clinically determined and laboratory confirmed that under the mask of ME/CFS is hidden still unknown chronic bacterial intoxication syndrome (CBIS), which develops as inflammation of chronic bacterial usually locally asymptomatic infection in kidneys, called nephrodisbacteriosis. For the first time it's determined clinical manifestations of CBIS caused by the action of neurotropic toxins with algic effect as well as psychotropic and dermatotropic toxins.

The implications/Conclusions: one of the typical clinical manifestations in patients with CBIS were symptoms and pathological states connected with the action of neurotropic toxins, including algic syndrome with such manifestations as trigeminal neuralgia, abdominal pain by type of solaritis, chronic pelvic pain and pain and stiffness in muscles by type of fibromyalgia. Some of the dominant clinical symptoms in patients with CBIS were also manifestations caused by the action of psychotropic toxins, including suicidal thoughts, and of dermatotropic toxins, including pertussis syndrome and alopecia.

Key words: chronic bacterial intoxication syndrome (CBIS), nephrodisbacteriosis, neurotropic toxins, algic syndrome, trigeminitis, solaritis, chronic pelvic pain, fibromyalgia, psychotropic

toxins, suicidal thoughts, dermatotropic toxins, alopecia, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Without stopping separately on the characteristics of each clinical variant of algic syndrome at CBIS, we will pay attention only to such important states in plan of diagnostics and treatment as trigeminal neuralgia, abdominal pain by type of solaritis, chronic pelvic pain and fibromyalgia.

The International Association for the Study of Pain (IASP) defines trigeminal neuralgia as a syndrome characterized by sudden short-term intense pain (from a few seconds to 2 minutes), recurrent, in the area of innervation of one or more branches of the trigeminal nerve, usually from one side. The symptomatic form of trigeminitis is very often associated with chronic herpes infection, which is caused by the herpes simplex virus type 1 (HSV 1). The pain is almost always unilateral and does not spread to the other side of the face and head, and is so painful and unbearable that it completely disrupts the normal rhythm of human life and in addition is poorly amenable to drug therapy.

Under our supervision there was 16/2340 or 0.7% of adults (women - 11, men - 5) with a diagnosis of trigeminal neuralgia, which in all patients occurred instantly almost without predictors and was unilateral. Because all patients were chronically affected by HSV 1, and 12 of them had additional HSV 2, all patients were initially suspected of having a herpetic nature of the lesion. In 7 cases after the use of intensive antiviral therapy there was obtained a very limited and unstable positive clinical result, in connection with which it was searched a possible additional or other cause of trigeminal nerve damage. Taking into account the previous experience of monitoring patients with algic syndrome of endotoxic origin, as well as the presence of a large number of symptoms of CBIS in these patients with trigeminitis, they were carried out bacteriological examination of warm urine and there were detected certain intestinal bacteria. There was established the diagnosis of nephrodisbacteriosis with the development of CBIS and dominant trigeminal neuralgia of endotoxic origin on the background of chronic HSV-infection in a latent state. During the first course of immunization with bacterial autovaccine, the intensity of pain in all patients decreased significantly, and after 2-3 courses - completely passed. During follow-up observation there were no recurrences of trigeminitis.

Abdominal pain by type of solaritis was observed in 7/2340 (0.3%) adults and in 3 children: in 1/750 (0.13%) - 5 years 6 months and in 2/870 (0.23%) - 7 and 9 years. Yes, it is indeed a very rare painful state, but the price of the question was very high, because the differential diagnosis bordered each time with surgical pathology. Especially this concerned children, in whom abdominal pain of any origin is usually localized in the umbilical region that primarily may imitate an attack of acute appendicitis. In these cases there was a risk of unnecessary surgery, as in our next observation.

Example 4

In the spring of 2015 the father and grandfather of a beautiful boy, let's call him Andrew, 7

years old, applied to the Vitacell Clinic. The day before, he was once again discharged from the surgical department, where he spent 3 days on suspicion of acute appendicitis. During the last year it was the seventh hospitalization on suspicion of appendicitis. Fortunately for the child, due to the uncertain clinical picture of these acute abdominal pain attacks, which had been repeated 2-3 times a month for a year and were localized around the navel each time, no hospitalization resulted in surgery. Although the surgeons' patience was clearly running out, because the boy had even been premedicated several times. According to relatives Andriy was already well known to surgeons in various profile departments of Kyiv, because he was probably released many times after an examination in the admission department and a general blood test, which usually remained almost "calm", although for some reason showed constant lymphocytosis instead of expected neutrophilia. The last time the boy was admitted to the surgical department, where almost 15 years ago I managed to prevent unnecessary appendectomy in several children with yersinic mesadenitis, which also largely imitated acute appendicitis, but quickly passed together with pain syndrome after Laevomycetinum. The head of the surgical department did not change, and after listening to the history of the wanderings of this suffering child, he advised to find and contact that infectionist.

Here's what happened. In early childhood Andrew was a sick child with a problematic nasopharynx, from which *St.aureus* was repeatedly isolated, and very often received antibiotics. From about 3 years of age parents began to notice frequent unexpected increase of temperature without catarrhal phenomena [I.M. - typical febrile attacks], which passed quickly, but left behind almost constant sub febrile, increased sweating, decreased hemoglobin (up to 105g/l), intoxication shadows under the eyes, increased irritability and uncontrollability of the child. Later on he began to complain of periodical joint pain, and from the age of 6 there was severe, sometimes unbearable abdominal pain, which recurred every 2-3 weeks. In the urine from the age of 3 years there were periodically noted minor proteinuria, leukocyturia and bacteriuria which were ignored. Taking in account the above mentioned, the boy was diagnosed with nephrodisbacteriosis and CBIS with recurrent abdominal pain by type of solaritis that was confirmed by the isolation of 3 urine-cultures of Enterococcus faecalis. There was prepared bacterial auto vaccine and was carried out immunization with a course of 10 injections. Already during vaccination and for the next 2 years of the follow-up observation there were no more abdominal pain attacks.

Chronic pelvic pain, which lasted in waves for more than 1 year, was observed in 28/2340 (1.2%) adults, more often in women (23/28 or 82%) in the absence of inflammatory processes or their latent state in the urogenital organs and in the thick part intestine. Pelvic pain had different localization: in the lower parts of abdomen below the navel, in the lower back and buttocks, as well as in the perineum, in the external genitalia, vagina, rectum. More often the patient could not reliably separate the primary point of pain, which had rather diffuse character, from near areas of its irradiation along the anterior and inner surface of the thighs and/or lower edge of the buttocks. The character of the pain was different: burning, tingling, prickly or aching pain, a feeling of pressure or heaviness. In some cases pelvic pain, which had a chronic course and moderate severity, could change suddenly and took on an unbearable paroxysmal character.

In 35/2340 (1.5%) patients (21 men and 14 women) muscle pain and stiffness dominated in the clinical picture of the disease by type of fibromyalgic syndrome or fibromyalgia. In 12 cases the diagnosis was established in the clinic, in 23 – on the primary long-term stages of treatment. Here is how some patients expressed their feelings, direct speech: "my body hurts as if beaten with sticks", "I was as if put on a spacesuit", "I'm like in a helmet", "I'm like wrapped in some armor", "muscles like stone".

Fibromyalgia (FM) is a disease with diffuse usually symmetrical musculoskeletal pain that has chronic character and significantly disrupts normal life of 2% to 8% of the population. It is noted that almost all patients with fibromyalgia have depression, which is considered as one of the consequences of FM. However there is still controversy about what is primary and what is derived: FM causes depression or depression leads to FM. Not all experts generally recognize such a diagnosis, as the origin of FM remains unclear. There are only dozens of hypotheses to explain the occurrence of FM (e.g., mental disorder, deep sleep disorders, poor blood supply and blood circulation in the muscles, even - mercury poisoning). But none of them was generally accepted. No signs of inflammation in the muscles and damage to internal organs cannot be detected at FM by modern diagnostic methods and in most cases the diagnosis is made by exclusion method.

The list of the main symptoms which are detected at FM, namely: widespread, often symmetrical pain in all body (in most cases - in muscles, sinews, joints) attracts attention; depression, poor sleep, lack of feeling of recovery after waking up; morning stiffness; rapid fatigue; headache, sometimes - like a migraine; swelling; often - a sudden sharp rise in temperature; feeling of numbness and tingling in various parts of the body; local convulsions and spasms of varying duration and severity; usually temporary impairment of concentration and memory, lack of ability to concentrate; in the expressed stage - stato-dynamic disturbances which change a little even during the day (impossibility to sit, stand and move normally); mental disorders; mood swings; also some remember dizziness, dryness and burning in the mouth, "irritated" bladder with frequent and sometimes painful urination.

Doesn't resemble anything? And so it is: the complete coincidence of symptoms for FM, CFS and CBIS is almost 98-100% that can hardly be an accidental or a simple coincidence. More over disputes about eggs and chicken (depression and FM) in this case lose their meaning. These are two equivalent in importance and severity states that are caused at CBIS by one reason: by severe endotoxicosis on the background of nephrodisbacteriosis or pyelonephritis. To some extent the very toxic origin may explain the appearance of many clinical symptoms at FM, which have not in its base morphological, biochemical and other disorders and common causes. Drug treatment of FM is carried out mainly as a symptomatic to relieve pain, muscle spasticity, irritability, sleep disorders and symptoms of depression, which gives an incomplete and unstable result.

All 35 patients under our observation apart from fibromyalgia noted increased weakness, fatigue, poor sleep, morning stiffness, headache, joint pain, low-grade fever and/or febrile attacks, bad mood, depression and many other symptoms typical for CBIS. Almost half of the patients (17/35 or 48.6%) had clinical manifestations of inflammatory processes in the genitourinary system

(urethroprostatitis, cystitis, colpitis, pyelonephritis), in 18/35 (51.4%) cases nephrodisbacteriosis was locally asymptomatic. Preliminary antiviral treatment of EBV, antibiotics, symptomatic and immunomodulatory treatment, rest at spas, massages etc. gave only a temporary positive effect, sometimes (after massage) - only for a few hours. During bacteriological examination of urine and warm urine in all patients there were isolated urine cultures of certain bacteria and it was carried out several cycles of treatment with bacterial auto vaccines. In 30/35 (85.7%) cases there was almost complete clinical remission in the course of both fibromyalgia and in general CBIS, which in 23/35 (65.7%) patients lasted from 3 to 5 years (observation period).

The other part of toxins caused functional lesions of the central nervous system, so that due to the dominant clinical manifestations they were considered as psychotropic. The effect of psychotropic toxins caused many different symptoms and syndromes, which usually dominated in the clinical picture of the disease in adult patients, less often - in children and teenagers. Among the main disorders of the central nervous system should be first of all noted the pronounced asthenic syndrome, which was noted by 100% of adults, 64.0% (557/870) of schoolchildren and 28.0% (210/750) of children from 3 to 7 years. All 100% of adults experienced rapid exhaustion unmotivated by physical or mental stress, which was also noted by almost 55% (478/870) of schoolchildren and 20.0% (150/750) of children aged 3 to 7 years.

Along with asthenic manifestations in patients with CBIS there were almost always present various cognitive impairments. Cognitive (informative) functions are called the most complex functions of the brain, through which the process of rational cognition of the world is carried out and there is provided purposeful interaction with it: perception, processing and analysis of information; memorization and storage; information exchange, construction and implementation of an action program, decision-making. All these vital functions, necessary for each person, suffered and disrupted to some extent under the influence of psychotropic toxins at CBIS. Onto impairment of memory, logical and associative thinking complained almost 79% (1848/2340) of adults and 39.0% (340/870) of schoolchildren, onto decreased concentration and attention - 80.0% (1872/2340) and 32.0% (279/870) respectively. Parents of even 18.0% (135/750) of children aged 3 to 7 years paid attention to this, although they usually attributed this to the age characteristics of preschool children. Many adults complained onto the impossibility of counting prime numbers freely and correctly. Here is how patients described their feelings in this state: "my head is not like mine", "I can't add 2 and 2", "I have as if cotton wool in my head", "I have some kissel in my head", “my head doesn't work"," I'm like a hedgehog in the fog - I don't understand where I am and who I am ".

For adults of various specialties (e.g., accountants, managers, brokers, stockbrokers, teachers and many others) it has become difficult or completely impossible to perform professional duties. A real decrease of mental abilities compared to the previous period of their lives was noted by 54.0% (1264/2340) of adults with CBIS. Parents of 15.0% (131/870) of children noted a significant deterioration in their academic performance: inability to recall previously studied material or learn new, tense relationships with teachers. And onto the remarks the son or daughter responded: "I

have no strength." Parents often did not believe this, sometimes insulting remarks were made, among which the "lazy" could be the mildest. But the child was not lazy and did not invent, she was really sick.

Along with the symptoms of general intoxication in patients with CBIS there were almost always emotional changes in domestic and social behavior. A calm and gentle person could become aggressive with unreasonable unmotivated outbursts of anger, annoyance onto almost secondary circumstances which were previously simply ignored. At the same time along with such uncontrolled excitement a person became easily vulnerable, resentful and tearful. Behavioral changes could also be further manifested by sudden unmotivated bad mood or unexpected euphoria. Decrease of life motivations and interest in surroundings were almost constantly noted by 88% (2059/2340) of adults and only 18.0% (157/870) of schoolchildren, it is understandable - they, despite of bad health, still had a vital supply of natural energy.

As a typical manifestation of the psychotropic action of toxins at CBIS can be considered the appearance of asociality, sometimes - just insurmountable. In almost 70% of adult patients there was partial or complete social maladaptation, bordering on sociality such as "do not touch me and I will not you." Cheerful, mobile and talkative people became closed, silent, contactless, preferring to sit still or lie down, not paying attention to their loved relatives, sometimes - even to their newborns. About a third of patients not only could not physically, but did not want to work at all to limit social contacts, and another third preferred to have only part-time employment.

The most characteristic for this state were often domestic and social indifference and apathy, which were noted by 82.0% (1919/2340) of adults and 14.0% (122/870) of schoolchildren. This is how some patients described their feelings. The 55-years-old woman says: "I always canned cucumbers and tomatoes for the winter, made compotes, cooked jams, closed more than 200 cans, because our family is big, and this year - none. Indifferently". A 30-years-old woman with tears in her eyes says: “We have a long-awaited child, she is now 6 months old, I tell my husband: go, take your daughter in your arms, you said that you love her so much, and he told me - keep it yourself, I do not have the strength, in general, I don't care now. " A 40-years-old woman says: “I just started ironing my clothes, I feel that my strength has run out, as if I had weeded 20 hundred square meters of garden, went to bed to rest. I see - I did not turn off the iron, standing on the linen, begin to smoke, and I lie down and simply look. Indifferently". A 60-years-old woman says: "In the morning I don't have the strength to get out of bed, cook breakfast and feed my family. I look - nearby is my husband, my grandchildren, I understand: it's my nearest people, I have to. But I don't have the strength and I don't care about them now."

Due to the general intoxication effect on the organism and in particular on the CNS, and taking into account the previously mentioned diagnostic, therapeutic and vital deadlocks in which patients found themselves, it becomes clear that almost 73% (1708/2340) of adults, 25% (218/870) of schoolchildren and 12% (90/750) of children from 3 to 7 years of age had multi-vector phobias. Patients with CBIS began to fear each his own, but more often cancer, especially in cases of such

previous diagnoses in close relatives. Or there was an insurmountable AIDS-phobia when patients "found" all the signs of AIDS in themselves and in their spouses and even in children. Continuing endlessly to take HIV-tests and blaming them for "infecting" their loved relatives, despite repeated negative results. Or with no less horror they began to be frightened by worms crawling under the skin or "brain-eating" toxoplasmosis or Epstein-Barr virus which "kills the immune system and causes cancer" and much other which today various oracles tell on the Internet about. Therefore very often we give our particularly frightened and receptive patients the same instructions that Professor Preobrazhensky gave to his young colleague Dr. Bormenthal in Mikhail Bulgakov's immortal novel "The Dog's Heart": "Never read Soviet newspapers before dinner." And in our case - never read any nonsense on the Internet, especially at night.

It was usually half a step from a phobia to a panic attack and depression. Gradually the vast majority of adult patients with CBIS (1732/2340 or 74%) and even 78/870 (9%) schoolchildren had panic attacks, especially at night, when sleeping, when a person woke up from some incomprehensible horror with a heart pounding in his chest, with shortness of breathing, wet with sweat and with the fear of imminent death. We have already mentioned the three deadlocks in which a patient with CBIS finds himself and which leads him to a phobic state, from which there was already a half step to depression, fear of death or vice versa - unwillingness to continue such a painful life.

It should be noted that depression is often combined with fear of death, usually remaining hidden from the view of close relatives and friends, sometimes - undisguised. A young woman, who 7 months ago gave birth to a wonderful healthy boy, came to our clinic. Having found herself in a serious state due to CBIS, the typical symptoms of which were clearly determined from her anamnesis and persisted for many years, the exacerbation of which was only provoked by physical and psychological exhaustion during pregnancy and childbirth, the woman was in a state of deep combined intoxication and postpartum depression. Talking about her symptoms and well-being, she suddenly cried softly and for almost 5 minutes nothing could stop her inconsolable sobs. To the remark that there is no reason for tears, that it is treatable and everything will be fine, she, continuing to cry and without raising her eyes, replied: "You don't understand anything. I feel like I'm dying. I'm dying and I can't even tell anyone about it, so as not to scare. Worse, I can't decide who take care of the baby after my death: mother or husband, husband or mother? "

On the other hand, in this psychologically horrible state more than a quarter of adults (655/2340 or 28%) and even 12/870 (1.4%) of schoolchildren had suicidal thoughts and reluctance to live so. Like this woman.

Example 5

In February 2014 a 45-years-old young woman came to the clinic. At that time the revolution of dignity had been going on in Kyiv for three months and the Maidan was raging, there were shooting, patriots were dying every day for Ukraine's independence. The woman entered the office by herself, ordering the man to sit in the waiting area. Despite the scorching cold outside, she

was wearing a light blouse and a white knitted hat. Pale tired focused face. She said that she lives far away - she lives permanently in one of the post-Soviet republics. From the woman's story it became clear that for the last 3 years she had suffered from CBIS, which was dominated by severe daily fatigue, exhaustion, low-grade fever, reduced work efficiency and sharply increased sweating, hair loss, constant joint pain and deep depression. The woman had typical fresh incisions on her forearms, which are usually left by suicides (I have seen these many times in patients when I worked in the AIDS unit). Intercepting my gaze, she leaned over the table and said in a confident, quiet voice: "Yes, you understood everything correctly. I do not want and will not continue to live like this, I'm tired. My last three years cannot be called life at all. It was just continuous torture. I can't be treated, I've tried many times. In vain. The husband knows nothing, so I left him downstairs. Six months ago, I tried to shorten my life, but it did not work. The owner of the apartment, which I rented for this purpose in another city, called an ambulance, I was rescued. Now I have come to you in Kyiv. Do you see a white hat on me? I have been walking along the Maidan for a month so that a sniper can hit me in the head. Many who were nearby me have already been killed. So that I go." The woman was silent, and I was silent. What to say? She is not a girl, her eyes are firm, the decision is balanced, she would unlikely change her decision and retreat. The thought flashed: if she did come, then maybe she still has hope, the last one? I said that I was thinking about her state and diagnosis, how it was being treated, and offered to be examined and then treated. As if hesitating a little, she agreed. The examination confirmed the diagnosis of nephrodisbacteriosis (3 cultures of Escherichia coli and 3 - fecal enterococci were isolated from the urine) with clinical manifestations of CBIS. There were prepared 3 vaccines, she said that she would be possible treated. Came out. But she returned almost a year later. She went into the office with her husband, smiling, her eyes open, friendly, she greeted me and it seemed as if she was going to come closer, as if she wanted to hug. I was even mentally ready to take a step towards her. She did not dare. She sat down and said that she had recovered, had no more complaints, felt her like she was born again, she lived a full happy life, took care of her little granddaughter and no longer thought about those nonsense.

In 12/2340 (0.5%) adults (women – 8, men - 4) with typical clinical manifestations of CBIS due to the influence of toxins of psychotropic action there was additionally observed a special mental state known as depersonalization/derealization syndrome. Patients noted such classic manifestations of this syndrome as constant or periodic, full or partial feeling of mental automatism, alienation, unnaturalness, unreality of the world around, some programming and predestination of their own movements, actions and thinking. The patient, being in such a state, reported that as if he did not belong to himself, did not live his life, but passively lived it, as if from the side watching himself, his movements, actions, that it was not him at all, because he is unable to control his body, his life, his feelings and emotions and lives as if in a fog or in a dream that does not end, but goes on and on. Also typical was a feeling of alienation, unreality of what was happening to them and around them, a feeling of being separate from a body, outside the body, not belonging to himself certain parts of the body (nose, ears, arms, legs) and inability to control them, as well as a combination of depersonalization/ de realization syndromes with a depressed state and the disappearance of the

diversity and multicolor of the world around them, which seemed to become all black and white, like an old movie. Direct speech: "I look at myself as if from the street through the glass", "my life seems to pass without me", "I do not belong to myself", "I feel myself separate from my body", "my thoughts seem to be generated not by my brain", "I seem to be asleep and can't wake up", "my soul seems to have left my body - I see myself from above", "in my life I am not a player, but a spectator", "my life is like an express train rushing past me, and I'm standing on a platform and I can't jump on it."

Patients were in this state from several months to 1-2 years, but none of them complained to the doctor, fearing that they would be misunderstood, disbelieved or declared mentally ill and sent to a psychiatric hospital. After starting treatment for CBIS during the first 1-2 months the clinical manifestations, caused by psychotropic toxins, and general toxic symptoms gradually weakened and partially or completely disappeared. There were no recurrences of depersonalization/derealization syndrome during the next 3-5 years of the follow-up observation.

Sometimes in 19/2340 (0.8%) adults, mostly young men aged 15-17 to 25-27, on the background of fobia and depressions there were mental disorders resembling manic-depressive syndrome or even partially signs of schizophrenia (without productive symptomatics) with negative symptomatics (decreased energy potential, apathy, lack of will) and cognitive disorders (disorders of thinking, perception, attention etc.). It becomes clear why more than half of adult patients - 1264/2340 (54%) and 44/870 (5%) of schoolchildren with CBIS in such a depressive state were consulted by a psychiatrist and often (725/2340 or almost 31% and 18/870 or 2% respectively) began taking antidepressants, which, however, usually did not give a noticeable overall positive clinical effect and scarcely improved the mental state of the patient.

Next for frequency and severity of manifestations in patients with CBIS were dermatotropic toxins, which caused such diverse and concomitant to symptoms of general intoxication damages as itching of the skin and mucous membranes, sometimes very severe, which was almost constantly complained of by 44% (1030/2340) of adults and 17% (148/870) of schoolchildren, nail brittleness and lesions (912/2340 or 39% of adults and 11/870 or 1.3% of schoolchildren). Constant or paroxysmal burning and a feeling of "sand" in the eyes, which caused moderate or insurmountable tearing, were noted by more than half of adults (1334/2340 or 57%) and 70/870 or 8% of schoolchildren. This feeling sometimes disappeared quickly simply after washing the eyes, during which they seemed to wash away the toxins that affected the conjunctiva. Periodically occurring or persistent feeling of obstruction in the throat was also noted by more than half of adults (1217/2340 or 52%) and sometimes - even schoolchildren (24/870 or 2.7%). At the same time instrumental examination of the thyroid gland and determination of its hormones, as well as other diagnostic searches did not find an answer to the cause of this symptom.

One of the frequent and clinically very debilitating manifestations of dermatotropic toxins action in patients of all ages with CBIS was a prolonged reflex cough, which was noted by 29% (679/2340) of adults, 25% (218/870) of schoolchildren, 19% (143/750) children aged 3 to 7 years and 7% (38/540)

of infants and under 3 years of age. The cough was not connected with inflammatory processes in the nasopharynx and/or respiratory tract and had presumably toxic origin due to irritation of the mucous membrane of the posterior pharyngeal wall and trachea by bacterial toxins. Such a dry unproductive cough, which was also called unmotivated, had stubborn and long-lasting character and could last from several months to several years. X-ray examination, CT, MRI of the lungs remained almost normal and could not clarify the causes of this cough, which very often (especially in children) had paroxysmal character, which was very similar to pertussis. And not only by the clinical picture, but also by the disappointing results of treatment: it could not be quenched by prescribing antibiotics or antispasmodics or expectorants. There was noteworthy that in all patients with reflex cough there was detected chronic Staphylococcal nasopharyngeal infection concomitant to CBIS. Just the combination of the chronic Staphylococcal infection with the main focus in the nasopharynx and of CBIS with the main focus in the kidneys generated this severe state of general and local intoxication, which could be called pertussis-like syndrome, which was more often misdiagnosed as pertussis. Just pertussis was usually ineffective for a long time treated in children and even in adults who had been in this state, often referring to "laboratory confirmation" of the diagnosis by detecting appropriate antibodies to the pathogen of this disease, unfortunately forgetting that these antibodies circulate for term of life in the blood after vaccination in childhood. Here is a pretty vivid example of such a pertussis-like syndrome in an infant.

Example 6

In winter 2012 the father of a 5-month-old boy, who was born and lived in one of the Scandinavian countries where his parents had been working for 3 years, applied to the clinic. He left the child at home with his wife because he was not sure that the child would survive the road to Kyiv in such a difficult state. A few years before the boy was born, his mother underwent an examination and treatment at the Vitacell Clinic from TORCH-infections due to a burdensome obstetric anamnesis and lost first pregnancy. Grateful parents named the boy Igor. So that in this family I already had some credit of confidence. The child had been coughing continuously in a row for 2 months. The cough got worse every night, became paroxysmal with signs of suffocation. The frightened parents, who had been sleeping one by one all this time, thought that the child might just suffocate. Local doctors treated the boy for pertussis (whooping cough) and prescribed antibiotics continuously, but they could do nothing: there was no improvement, the cough did not stop. The father said that before the cough the child had one case of a cold with consequent prolonged discharge of mucus from the nose, sometimes there was a low temperature (37-37.2°C), a moderate rash on the skin and there was noted increased sweating of the child. And already during coughing and treatment with antibiotics there were twice "not very good" urine tests: "ran" slightly elevated leukocytes, found traces of protein. In absentia, clinically, the child's state was estimated as nephrodisbacteriosis and CBIS with a dominant prolonged reflex cough as a manifestation of dermatotropic toxins action on the background of Staphylococcal infection of the nasopharynx. The father brought with him a vaccine made from the museum's previously isolated autostrains of Staphylococcus. And onto the warning that local doctors would unlikely introduce it, the father who was a veterinarian said, he

would stab the child himself. After the second injection of the vaccine the cough noticeably calmed down, the child and parents were able to sleep partially at night, and after the 5th injection it stopped completely and did not return anymore. When the child was 3 years old, he and his parents came to Kyiv and the whole family visited the clinic. Clinically the boy was healthy.

Another frequent manifestation of dermatotropic toxins influence on the organism of patients with CBIS was increased hair loss and alopecia and bacterial toxicoderma, which could dominate in the clinical picture of the disease and for some time seemed to have an independent nosological diagnosis. It should be noted that many patients with CBIS paid attention onto increased hair loss. More than half of adults (1240/2340 or 53%), mostly women, and even 3% (26/870) of schoolchildren noted that hair "spills", "became thin", "falls out by shreds", "so soon the head will be completely hairless." In 92/2340 (3.9%) adults, among whom women significantly prevailed (68/92 or 73.9%), as a result of such a gradual increased hair loss, less often - suddenly, developed alopecia. Clinical variants of alopecia were different: from focal (nest or focal) to subtotal and even total. The first foci of alopecia more often appeared on the head, and only then in some patients in the eyebrows, eyelashes and beard. Focal alopecia was characterized by the appearance of one or more foci of alopecia. With subtotal alopecia on the head remained small areas of growing hair, and with total alopecia the entire scalp was "naked". Universal alopecia characterized by hair loss not only on the head but also all over the body, in patients with CBIS there was not observed.

The results of treatment of patients with alopecia on the background of CBIS directly depended on the age of alopecia and persistence of patients in the use of bacterial vaccines and only in the last place - on prevalence of alopecia. The best results were obtained in cases of short-term previous course of alopecia (from 1 to 3 years) and after 2-3 cycles of immunization for 2-3 courses each. Treatment by bacterial vaccines underwent 75 patients with CBIS with focal, subtotal and total alopecia, who had previously been persistently and usually repeatedly treated with the usual in such cases courses of "restorative" treatment with limited and unstable positive clinical result. In 63/75 (84%) cases there was achieved a noticeable positive clinical effect: hair began to grow again, and in 51/75 (68%) patients even with total alopecia the hair layer was completely restored.

Here is just one good example.

Example 7

A 35-year-old woman went to the clinic for her first consultation at the end of winter in 2014. After removing her wig from her bald head, she sadly said with tears in her eyes: “I have had such a “knee” for a whole year. Nothing helps." She said that she had already undergone 4 long courses of treatment at various doctors-trichologists and now she does not know whether it makes sense to continue to look for "her" doctor who will help. In this last remark there was a certain distrust of the patient to the doctors, which was understandable. During the consultation it was found that in addition to total alopecia, the patient for several years before felt increased fatigue, weakness, joint

pain, almost constantly had a sub febrile temperature, could not do anything with a bad mood, apathy, every day in the mirror saw dark circles and puffiness under the eyes. For a long time the woman struggled with increased hair loss, which eventually led to a complete baldness of the head almost a year ago. From the anamnesis it was also established that since school age the woman suffers from chronic often recurrent cystitis. The previous diagnosis of nephrodisbacteriosis with the development of CBIS with clinically dominant total alopecia was confirmed by bacteriological examination of 3 portions of warm urine, from which 3 urinary cultures of *E.colli* were isolated. During the next 12 months there were performed 2 cycles of immunization with bacterial vaccines with auto strains per 3 courses each. Over 6 months after the end of treatment in early autumn 2015 the woman came for regular consultation. Sitting in front of me, radiant, with beautiful hair, she leaned forward a little and said quietly: "Pull me by the hair, well, pull me, please. These are mine, my own. I whisper because I'm afraid of telling: I've already been to the hairdresser three times."

Another 12/75 (16%) patients after the first course of vaccination with a positive clinical effect and partial recovery of lost hair for various reasons discontinued treatment and their subsequent fate was unknown. In the other 12/75 (16%) cases of subtotal and total alopecia, which lasted from 3 to 10 years, neither a doctor nor a patient saw a noticeable positive clinical result after the first course of treatment: hair growth did not resume. Therefore subsequent courses of treatment with bacterial vaccines for these patients were not performed. It is possible that in these cases a known effect worked, when the long existence of such nests or total alopecia was able to lead to dystrophic changes in the hair follicles with their subsequent complete atrophy.

It should be noted that after the cessation of action of the aggressive toxic factor, both exogenous (in case of poisoning by pesticides, thallium, mercury) and as in our cases of endogenous origin, hair loss stops. Fortunately, diffuse alopecia of toxic origin is usually a reversible process, and new hair usually grows in place of the fallen hair. It should be noted that focal alopecia is considered by some doctors as a purely autoimmune disease. This is difficult to agree with it, especially taking into account the experience of complete hair restoration in patients with nephrodisbacteriosis and CBIS who have undergone several cycles of immunization with bacterial autovaccines and have not been treated at all with immunosuppressive drugs.

The Implications/Conclusions

1. There is shown the clinical picture of such important in terms of diagnostics and treatment manifestations of algic syndrome at CBIS as trigeminal neuralgia with clinical manifestations of trigeminitis in 16/2340 adults or 0.7%, abdominal pain on the type of solaritis, which was observed in 7/2340 or 0.3% of adults and 3/870 or 0.34% of schoolchildren, chronic pelvic pain (in 28/2340 or 1.2% of adults). In 35/2340 (1.5%) adults in the clinical picture of the disease dominated muscle pain and stiffness by type of fibromyalgia or fibromyalgia syndrome.

2. The clinical manifestations of action of psychotropic toxins in patients with CBIS, which usually dominated in the clinical picture of the disease in adult patients, less often - in children and teenagers, included a pronounced asthenic syndrome, which was noted by 100% of adults and from 28% to

64% of children from 3 up to 14 years, rapid exhaustion (100% and from 20% to 55%, respectively). Along with asthenic manifestations in patients with CBIS there were almost always present various cognitive disorders: 79% of adults and 39% of schoolchildren complained of memory impairment, logical and associative thinking; 80% and 32% respectively and even (according to parents) - 18% of children aged 3 to 7 years complained of decreased concentration and attention; 54% of adults and parents of 15% of schoolchildren, who began significantly to lag behind in school, noted decrease in mental abilities in comparison with the previous period.

3. One of the main manifestations of action of psychotropic toxins, which were found in more than ¾ adult patients with CBIS, were emotional changes in domestic and social behavior: a decrease of life motivations and interest in the surroundings was noted by 88% of adults and 18% of schoolchildren, domestic indifference and apathy – by 82% and 14% respectively; almost in 70% of adults developed partial or complete social maladaptation, bordering on asociality. In 73% of adults, 25% of schoolchildren and 12% of children from 3 to 7 years of age developed multi-vector phobias with subsequent development in 74% of adults and in 9% of schoolchildren of panic attacks, fear of death or vice versa - reluctance to continue such painful life: 28% of adults and even 1.4% of schoolchildren had suicidal thoughts. In 12/2340 (0.5%) adults with typical clinical manifestations of CBIS, due to the influence of toxins of psychotropic action, there was observed the occurrence of such a special mental state as depersonalization/derealization syndrome. In 19/2340 (0.8%) adults, mostly young boys aged 15-17 to 25-27 years, on the background of phobias and depressions there were mental disorders resembling manic-depressive syndrome or even incomplete signs of schizophrenia. More than half (54%) of adult patients and 5% of schoolchildren with CBIS with additional manifestations of action of psychotropic toxins visited a psychiatrist, and 31% and 2% respectively began taking antidepressants, which usually scarcely improved their mental state.

4. The next in clinical frequency and severity of manifestation in patients with CBIS were dermatotropic toxins, which caused such various and concomitant to symptoms of general intoxication lesions as itching of the skin and mucous membranes (in 44% of adults and 17% of schoolchildren), fragility and nails lesions (39% and 1.3%, respectively), constant or paroxysmal burning and a feeling of "sand" in the eyes, which caused moderate or insurmountable tearing (57% and 8%, respectively), a feeling of obstruction in the throat (52% and 2.7 % respectively).

5. A frequent and clinically very debilitating manifestation of action of dermatotropic toxins in patients of all ages with CBIS was a prolonged reflex cough, which was noted by 29% of adults, 25% of schoolchildren, 19% of children aged 3 to 7 years and 7% infants and under 3 years of age. Such a dry, unproductive and unmotivated cough, which had often paroxysmal character, was not connected with inflammatory processes in the nasopharynx and/or respiratory tract and had toxic origin, was persistent and long-lasting and could last from several months to several years. Usually the combination of CBIS with concomitant chronic Staphylococcal infection in the nasopharynx generated this severe state of general and local intoxication with reflex cough, which could generally be called as pertussis-like syndrome, which however was more often misdiagnosed as pertussis.

6. Increased hair loss and alopecia were frequent manifestations of influence of dermatotropic toxins in patients with CBIS. Increased hair loss was noted by more than half of adults (53%), mostly women, and even by 3% of schoolchildren. In 92/2340 (3.9%) adults, among whom mostly dominated women (68/92 or 73.9%), in a result of such increased hair loss, less often - suddenly, developed alopecia with different clinical variants: from focal (nest or focal) to subtotal and even total. The best results of treatment with bacterial vaccine, which underwent 75 patients with CBIS with focal, subtotal and total alopecia, were obtained in cases of short-term previous course of alopecia (from 1 to 3 years) and after 2-3 cycles of immunization. In 63/75 (84%) cases there was achieved a noticeable positive clinical effect: hair began to grow again, and in 51/75 (68%) patients even with total alopecia the hair layer was completely restored.

Report 5: Clinical Diagnosis

Abstract

Objective: Of the research was to continue the study of clinical manifestations of chronic bacterial intoxication syndrome (CBIS), caused by the action of dermatotropic, arthromyotropic and ophthalmotropic toxins.

Design: Of the research was as previously clinical-diagnostic and included the determination of clinical manifestations of such a still unknown disease, which was called chronic bacterial intoxication syndrome (CBIS), which has long been under the mask of a diagnosis of ME/CFS. The studies were prospective-retrospective and were longitudinal. The effectiveness of the obtained results of the study had direct character, because they undoubtedly led to the improvement of the patient's state and life.

The style of presentation of the material is narrative, not tedious.
Conditions: the researches were multicenter and conducted in ambulant conditions on the basis of 2 clinics specialized in the field of chronic infectious diseases with a full range of laboratory studies.

Participants: all patients who seeked advice in clinics during 2009-2020 with complaints consistent with a diagnosis of CFS, which was previously diagnosed in almost a third of patients on former stages of examination and treatment.

Results: Report 5 continues to consider the clinical manifestations of CBIS in 4500 children and adults according to the Table 1 in Report 2, namely the clinical symptoms and pathological states caused by dermatotropic toxins - bacterial toxicoderma, which were observed in 222/540 (41%) of children under the age of 3 years, in 398/750 (53%) - from 3 to 7 years, in 392/870 (45%) - from 7 to 14 years and in 889/2340 (38%) adults. Skin lesion was almost always combined with other symptoms of CBIS, although it often noticeably dominated in the clinical picture of the disease. Clinical manifestations of CBIS caused by arthromyotropic toxins, algic manifestations of which from the joints, spine and muscles were partially considered earlier in Report 3, included reactive arthritis (ReA), which were observed in 770/4500 (17.1%) patients with CBIS. There were

540/2340 (23%) adults, 157/870 (18%) schoolchildren and 73/750 (9.7%) children aged 3 to 7 years. It was found that ReA were not connected with previous acute intestinal and sexually transmitted infections, as well as with chronic genital chlamydia, but ReA developed on the background of chronic bacterial infection in the kidneys - nephrodisbacteriosis, rarely - manifest pyelonephritis that led to the development of CBIS with dominated joint damage, which was misdiagnosed by other diagnoses. A part of the bacterial toxins at CBIS had an ophthalmotropic effect, with which there were connected such clinical states as toxic conjunctivitis of endogenous origin, observed in 211/2340 (9%) adults and 18/870 (2%) schoolchildren, toxic uveitis of endogenous origin, which was diagnosed in 24/4500 (0.53%) patients, retrobulbar optic nerve neuritis, which was observed in 5/2340 (0.57%) and transient diplopia, which developed in 7/2340 (0.3 %) adults. It was found that in almost 100% of children and 50-70% of adults with CBIS there was a concomitant chronic Staphylococcal infection, the primary focus of which was in the nasopharynx that introduced into the clinical picture of the disease typical for this infection additional clinical symptoms. It was established that in 63% of adult patients and 73% of children at the moment of diagnosing them CBIS they had nephrodisbacteriosis in "pure" form without any signs of inflammatory process in the kidneys. There was established such a characteristic clinical circumstance as the existence of monosymptomatic CBIS, which had not just a dominant, but almost only one manifestation that had to be taken into account when establishing the appropriate diagnosis.

The known: existence of a diagnosis ME/CFS with an unknown etiological cause.

The new: for the first time it's clinically determined and laboratory confirmed that under the mask of ME/CFS is hidden still unknown chronic bacterial intoxication syndrome (CBIS), which develops in patients with CBIS on the background of inflammatory focus of chronic bacterial usually locally asymptomatic infection in kidneys, called nephrodisbacteriosis. For the first time it's determined clinical manifestations of CBIS caused by the action of dermatotropic, arthromyotropic and ophthalmotropic toxins.

The implications/Conclusions: one of the typical clinical manifestations in patients with CBIS were symptoms and pathological states connected with the action of dermatotropic, arthromyotropic and ophthalmotropic toxins of bacteria on the background of the focus of chronic bacterial infection in the kidneys (nephrodisbacteriosis).

Key words: chronic bacterial intoxication syndrome (CBIS), nephrodisbacteriosis, bacterial toxicoderma, reactive and rheumatoid arthritis, ophthalmotropic toxins, toxic conjunctivitis, toxic uveitis, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Among the symptoms and diseases that were connected with the action of dermatotropic toxins in patients with CBIS, it should be noted a very frequent direct skin lesion with the appearance of various variants of dermatitis, which, despite different names, combined one common pathogenetic cause: they were caused by bacterial toxins of dermatological direction. Bacterial toxicodermas were more often observed in children: at the age of 3 years - in 222/540 (41%) cases, at the age from 3 to 7 years - in 398/750 (53%), from 7 to 14 years - in 392/870 (45%) and in 889/2340 (38%)

adults. Skin lesions were almost always combined with other symptoms of CBIS, although they often noticeably dominated in the clinical picture of the disease.

Wikipedia interprets toxicoderma as "acute inflammation of the skin under the influence of substances that enter inside the body and have allergic or toxic-allergic properties." It is emphasized that the etiological factor in this case penetrates the skin by hematogenous way, and the main role is played by exogenous toxins. However it is noted that there is also an endogenous cause of toxidermia, namely "autointoxication by unusual metabolic products that appear in the organism due to dysfunction of the gastrointestinal tract, liver, kidneys."

Under the term bacterial toxicoderma it had in view acute or chronic irritation or inflammation of the skin caused by bacterial dermatotropic toxins of bacteria that cause nephrodisbacteriosis and/or pyelonephritis and CBIS. That is the main focus of the formation of bacterial toxins that irritate and affect the skin, in 100% of cases of such diseases were the kidneys. It should be noted that like the focus in the kidneys, so and two foci of chronic bacterial infection played a significant role in the occurrence of toxicoderma. One of them was located in the nasopharynx, was primarily connected with Staphylococcus aureus and was found in 100% of patients with CBIS with skin lesions. Another focus, concomitent to bacterial toxicoderma origin, in which there were produced dermatotropic toxins, was the intestine, especially in cases of dysbacteriosis in it, that was more often determined and had an important role in infants and the first 3-5 years of life.

Bacterial toxicoderma could be additionally provoked and exacerbated also by external factors (trigger factors) of toxic or toxic-allergic character, which entered the organism through the digestive tract, respiratory tract or with parenteral (intravenous, intramuscular or subcutaneous) administration. Toxicoderma differs from other dermatitis by those that the provoking agent got not directly on the skin, but penetrated it along with the bloodstream - that is hematogenously. The lymphogenic way of distribution of bacterial toxins is not also excluded. Trigger factors that externally give the formally main or additional impulse to the clinical manifestation of the disease, usually trigger the already formed, but till the time being latent "dormant" process of skin damage by toxins of bacterial origin, sensibilization to which could accumulate over the years.

Bacterial toxicoderma was one of the most frequent manifestations of CBIS and they were noticed in more than a third of adults and almost half of children. If some say that the tongue is a mirror of the gastrointestinal tract, then there is such a clear impression that the skin is a mirror of the kidneys. Clinical dermatological diagnoses, established for patients with CBIS, included such more often nosologically separated diseases as just actual toxicoderma (spotted, papular, nodular, vesicular, pustular, bullous), atopic dermatitis and other variants of dermatitis (neurodermatitis, contact dermatitis, allergic dermatitis, seborrheic dermatitis), erythema (migratory, annular, multiform exudative), urticaria, local asymmetric Quincke's edema usually on the face (lips, eyelids), eczema, psoriasis, erysipelas. That is all these diagnostically stable diseases were considered as different clinical variants of bacterial toxicoderma, which occured on the background of nephrodisbacteriosis/pyelonephritis and was only one of the manifestations of CBIS. Such an unusual view on the nature of these skin diseases, many of which are usually considered genetically

determined and/or hereditary, i.e. read - incurable, has changed the strategy and tactics of their treatment. Namely: it was not treated skin and allergies, but CBIS, which caused damage to various organs and systems of the organism, including the skin. This approach to the treatment of these various skin lesions and to their treatment maximally without the use of anti-allergic, hormonal drugs and antibiotics with prescribing of bacterial vaccines allowed to achieve effective treatment in children, in particular such diseases as atopic dermatitis, eczema, psoriasis at the level 80-100%. But usually only in children. In adults who have lived with these diagnoses almost all their lives, the most that could be expected is to achieve more or less stable remission. Although in cases of treatment in adults with disease experience up to 3 years, the results were also much better. Detailed the results of treatment will be considered in the following reports of CBIS. And now here is one of the many encouraging examples of such a successful treatment.

Example 8

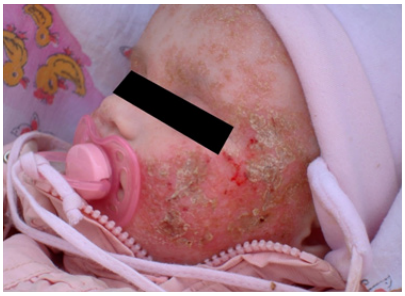
The child Marichka, whose parents went to the clinic in December 2008, when the child was 3 months old, with complaints of unformed defecation of green color with mucus, poor sleep, pressing the legs to the abdomen, screaming and anxiety of the child. Identical strains of *Staphylococcus aureus* were isolated from feces, nose and pharynx. Due to the absence of systemic manifestations of staphylococcal infection, as well as taking into account the infant's age and parental wishes, there was carried out only local treatment of nasopharynx and intestinal dysbacteriosis, after which the child's state clinically improved. But in the near future at the age of 6 months, first on the skin of the face, and then very quickly completely on the corpus and extremities, appeared a rash, which was verified by dermatologists as atopic dermatitis (genetically determined - hereditary) with elements of wet eczema. The child was prescribed treatment, in accordance with the existing protocol, with corticosteroids and antibiotics, but before such treatment, Marichka's parents came to our clinic again.

At bacteriological research again from the nasopharynx and feces, and additionally from different affected areas of the skin, as well as from urine, there were isolated identical strains of Staphylococcus aureus. The level of total IgE within 3months increased in the child from 2 to 110 IU/ml (age norm - up to 10IU/ml). There were carried out 2 courses of immunization with staphylococcal auto vaccine (each - 10 injections). During the next 6 months from the beginning of treatment it was noted a positive clinical dynamics: the skin was completely cleansed of the elements of the ras. The level of total IgE without prescribing of anti-allergic drugs decreased to 19 IU/ml. During the next 11 years of observation (on September 25, 2020, the child was 12 years old) there were no more recurrences of atopic dermatitis, the child's skin remains smooth as an Easter egg. The diet was not followed; there were no restrictions in nutrition and lifestyle. For a long time almost professionally she goes successfully in for sports on a tennis court.

Previously there were considered such typical algic states as arthralgia, spondylalgia and myalgia, including fibromyalgic syndrome, which were attributed to clinical manifestations of CBIS, caused by arthromyotropic toxins. Special attention should be paid to such a serious disease as reactive

arthritis (ReA), which was also considered to be a consequence of the action of arthromyotropic toxins of bacteria in patients with nephrodisbacteriosis and pyelonephritis.

Currently it's accepted that ReA includes inflammatory non-purulent joint diseases that develop as a result of immune disorders after acute intestinal infection (in 1.5-4% of cases) and more often, according to persistent notions, caused by toxins of such enterobacteria as Yersinia, Salmonella and Shigella, as well as urogenital infections transmitted sexually (1-3%), among which 80% of cases are associated with Chlamydia trachomatis, explaining it as a "pandemic of chlamydia in the world." Etiologically ReA is also associated with some respiratory infections, namely with Mycoplasma pneumoniae and Chlamydia pneumoniae, which as though may also be responsible for the development of ReA. This statement, in our opinion, looks at least strange. Taking into account our 25-years' experience of clinical observation for patients with these purely pulmonary infections, they have never caused reactive arthritis. It should be separately emphasized that both pulmonary and urogenital mycoplasmas and ureaplasmas are harmless. Taking into account the clinical experience for the same period of observation and treatment of patients with urogenital inflammatory diseases, it can be stated that these sexually transmitted infections are generally saprophytic flora and never, in nobody and under no circumstances do not cause inflammatory urogenital diseases and moreover they cannot be the triggered factor of the emergence of ReA, as reported by some sources (Figure 1 and Figure 2).



For some reason, rather wrong, even Klebsiella pneumoniae is considered to be one of the infectious agents of respiratory tract, which, according to some reports, can also cause ReA. Probably because this typical intestinal bacterium, which lives for life in the intestines of every person and remains there saprophytic, historically has name Klebsiella pneumonia. When changing the territory of stay on all other mucous membranes, including the respiratory system, Klebsiella can cause severe purulent inflammatory processes. Reactive changes of non-purulent character in the joints, associated with Klebsiella, are quite possible, but only in cases of its persistence in the kidneys at nephrodisbacteriosis / pyelonephritis.

Neither in the available medical literature, nor in the Internet, nor in previous and current classifications of reactive arthritis, nor in WHO reports there is no information that the source of

primary infection, which is a trigger factor for the secondary development of reactive arthritis, may be found in the kidneys. It has not been also found that the pathogens of ReA can be usual naturally symbiotic and saprophytic enterobacteria and enterococci that live in the human intestine for life, as well as pathogenic staphylococci and streptococci, in cases of forming by these bacteria a focus of chronic bacterial infection in the kidneys.

It should also be noted the following. From the literature concerning ReA it is known that more than once there have been revealed the facts of acute lesions of the intestine and/or genitourinary tract not only as primary in relation to ReA, but with the possibility of development simultaneously with it and even after joint damage. This violates the "established" causal links and makes the generally existing statement that ReA is the result of acute sexually transmitted and intestinal infections simply illogical. And another strange circumstance. It cannot be in etiological plan principally different causative agents for the same disease in children and adults, such as sinusitis, or bronchial asthma, or pyelonephritis, or all other human diseases of infectious origin. Then where is the chlamydial etiology of the origin of ReA in children who also suffer from ReA, which is a trigger factor as if for 80% of diseases in adults? In children who do not even realize the meaning of words sexual life, but you see - are ill?

During the last 11 years (since 2009) under our supervision and treatment there were 770/4500 (17.1%) patients with CBIS on the background of nephrodisbacteriosis and/or pyelonephritis with a dominant in the clinical picture of the disease reactive non-purulent inflammation of the joints. There were 540/2340 (23%) adults, 157/870 (18%) schoolchildren and 73/750 (9.7%) aged 3 to 7 years. Usually, diagnoses of joint damage were established at the previous stages of examination and treatment: reactive arthritis - in 560/770 (72.7%) cases (in another 70/770 or 9.1% of cases the diagnosis of ReA was initially established in our clinic), rheumatoid arthritis (RA) - 70 (9.1%), including juvenile RA in 9 children (1.1%), as well as arthritis on the background of gout - 45/770 (5.8%) cases, psoriasis - 15/770 (1.9%) and joint damage that occurred on the background of borreliosis (Lyme disease) - in 10 patients (1.3%), that totally amounted also 70/770 (9.1%) cases. Reiter's syndrome on the background of nephrodisbacteriosis developed in single cases - only in 12/770 (1.5%) patients. Changes in the skin and mucous membranes at Reiter's syndrome, which occurred in the form of keratoderma and painless ulcers on the genitals, were considered as a classic bacterial toxicoderma, which was very often detected at nephrodisbacteriosis even without joint damage.

Among patients with ReA, adults predominated (540/770 or 70.1%), although there were many children - almost a third (230/770 or 29.9%). In 747/770 (97%) cases joint disease was chronic and lasted more than 1 year. It should be once again emphasized that in all 770 patients with joint damage who were observed, reactive arthritis developed not after acute genital and/or intestinal infections, as it is usually reported when this diagnosis is made. Furthermore in all adults there were ruled out (by ELISA and, if necessary, PCR) chronic infection with genital chlamydia. ReA developed on the background of a chronic bacterial infection in the kidneys - nephrodisbacteriosis, less often - manifest pyelonephritis, that led to the development of CBIS with the dominant in these cases joint damage, which was incorrectly given other diagnoses.

In patients with gout, psoriasis and Lyme disease treatment of arthritis with bacterial vaccines with a rapid and relatively stable positive clinical result without the use or with discontinuation of drugs use, usually prescribed to patients with such diagnoses, ex juvantibus confirmed the primary role in the joint damage of toxins of bacteria which caused nephrodisbacteriosis and/or pyelonephritis. At the same time fairly often there was such a paradoxical situation, when in patients as if with gouty arthritis the level of uric acid decreased or remained within normal limits, but inflammation of the joints continued to progress. And conversely: with significantly elevated levels of uric acid after treatment with the bacterial vaccine, joint pain completely disappeared. An example of effective treatment with bacterial vaccines of a patient with gout whose polyarthritis during 10 years did not respond to standard in such cases treatment and therefore it was already planned to prescribe him therapy with cytostatic drugs, was given earlier (see Example 1 in Report 1). Here are two more examples: of the successful treatment of a young man with bacterial vaccines, whose reactive arthritis during 2 years of a "protocol" therapy seemed to be insurmountable, and of rheumatoid arthritis in a small child - in each example everything that happened had big chances to end by complete disability of patients.

Example 9

A 35-years-old man went to the clinic in the spring of 2017. He has been suffering for 2 years with very severe pain in the asymmetrical joints of the upper and lower extremities with their periodic deformation. There was diagnosed reactive arthritis without determining the etiological factor: on the eve of the onset of joint pain during 6 months there were no episodes of acute infectious diseases of the genitourinary system and intestines. Almost continuously throughout the disease he has been taking nonsteroidal anti-inflammatory drugs (NSAIDs) in medium-high doses, and attempts more than once to discontinue the drugs and even reduce the dose have exacerbated ReA with recurrence of pain and the accession of new joints damage. Additionally during the examination at the clinic the patient complained of constant low-grade temperature, weakness, decreased vital energy, headache, intermittent dizziness, increased sweating, decreased tolerance to physical and sports activities, long-term hypochromic anemia. He hasn't worked for almost a year, he is lame, he walks with a cane. A doctor recommended him to register a disability group because the "prognosis is disappointing." From the anamnesis it was also established that almost 7 years ago he underwent the debut of acute pyelonephritis, which until now remained in a complete long-term clinical latency; monitoring of general urine analysis has not performed.

Examination in the clinic revealed moderate proteinuria (0.066 g/l), leukocyturia (8-10 in p/s), single altered erythrocytes and granular cylinders, bacteriuria. Bacteriological examination of warm urine (within three days in a row there was isolated an identical culture of Enterococcus faecalis) confirmed the diagnosis of nephrodisbacteriosis with the debut of pyelonephritis in the distant anamnesis with the development of CBIS and the dominant picture of secondary reactive arthritis. There was prescribed a cycle of treatment (with two courses of 10 injections each with an interval of 1 month between courses) with bacterial divalent Escherichia coli+enterococcal

autovaccines, which gave the closest positive clinical results. The dose of NSAIDs was significantly reduced (without deterioration of the general state and without recurrence of arthritis), joint pain almost disappeared, he returned to work. 2 months after the end of the first cycle of vaccination there was a recurrence of ReA, but with less pain. After control urine culture examination (there was isolated culture of *E.coli*) there was prescribed a second cycle of vaccination. Currently (September 2020) he has passed 5 cycles of vaccination, NSAIDs for almost 2 years does not apply at all, has no complaints, works, regularly trains in the gym. There have been no recurrences of ReA for more than a year. He remains under supervision and undergoes periodic bacteriological examination of urine.

Example 10

A 3-years-old boy, let's call him Andriyko, has been ill for almost a year. The child's parents went to the Vitacell Clinic in early 2006. The diagnosis, which was made to the child at the place of residence in one of the southern regional centers of Ukraine, sounded like a sentence to the parents: juvenile rheumatoid arthritis. According to local doctors, the detection during the child's genetic examination of HLA-B27 antigen explained the severe course of the disease and significantly worsened its prognosis. The joints of the lower extremities were mostly affected; the child had not walked for 4 months: the father carried the boy in his arms to the cabinet. From the very beginning of the disease the child was on glucocorticosteroid therapy in a medium-high dosage, but the inflammatory process in the joints almost did not stop and with each subsequent recurrence the situation only worsened. The parents were reasonably told that they had to prepare for the worst and that the child would most likely become completely disabled in the near future, because "it all started very early." During the examination of the child in Kyiv there were revealed additional symptoms such as a prolonged sub febrile, increased sweating, from the anamnesis it was found out predisposition to frequent colds with the development of acute sinusitis 6 months ago, prolonged decrease of erythrocytes and leukocytes, periodic rash on the skin by type of recurrent urticaria and atopic dermatitis. Parents mentioned that the child sometimes had frequent urination, which neither they nor the doctors associated with joint damage.

On the basis of bacteriological examination of urine (three days in a row) with the isolation of three strains of *E.coli* and three strains of Enterococcus faecalis, as well as smears from the nose and throat (isolated St.aureus) there was diagnosed: nephrodisbacteriosis (Escherichia coli + enterococcal), locally asymptomatic with dominant secondary reactive arthritis and concomitant chronic staphylococcal nasopharyngeal infection with frequent colds and recurrent rhinosinusitis. Hormone-dependent form of juvenile rheumatoid arthritis? There was prescribed a course of sequential treatment with three bacterial autovaccines: first staphylococcal - with 7 injections, then 10 injections Escherichia coli + enterococcal with 3 autostrains of *E.coli* and 3 Enterococcus faecalis, and finally – 10 injections with a polyvalent vaccine made of own strains of bacteria. Already during the first cycle of treatment the child stood up on his feet, began to walk independently, subfebrile disappeared, stopped giving prednisolone. During the next two years there were carried out in a total 3 cycles of treatment with bacterial vaccines: recurrences of inflammation in the joints stopped, the child fully recovered. The follow-up observation lasted 10 years (until 2015 - then the

connection was interrupted), there were no more recurrences of arthritis. Many times the child's mother was asked to appear on one of the TV channels and to tell the story of the child's wonderful recovery in order to give hope to other parents of such children with "rheumatoid arthritis", but she refused saying "I'm afraid to bring misfortune."

It is often emphasized that in real practice the term ReA is mistakenly used much more broadly and to the term ReA are included arthritis of other etiology: after a viral infection, post-vaccination arthritis, post-streptococcal arthritis and some others. Therefore in our case, it is either a previously unknown variant of reactive (sterile) joint damage on the background of chronic infection of kidneys (nephrodisbacteriosis and pyelonephritis), or simply patients with diagnoses of secondary reactive non-purulent arthritis, regardless of the root cause, were not previously examined bacteriologically for the presence of bacteria in their kidneys.

The state is not determined: the diagnosis and treatment of many patients with ReA, and possibly with RA and other variants of non-purulent arthritis, do not correspond to the true etiological cause of their disease. Despite the almost constant, sometimes lifelong use of various drugs, most of which have harmful side effects, joint damage usually only progresses, almost unresponsive to attempts to stop them, with a high risk of disability of such patients.

Among the clinical symptoms of CBIS, listed in the Table 1 (see Report 2), remain unconsidered lesions caused by ophthalmotropic toxins: conjunctivitis, uveitis, optic nerve neuritis and diplopia.

Infectious lesions of the mucous membrane of the eye (conjunctiva) can have a viral, bacterial or toxic nature. The most spreaded and studied - are viral and bacterial (purulent) conjunctivitis. Conjunctivitis caused by effect of toxic substances of exogenous origin is called toxic conjunctivitis. The development of this type of conjunctivitis occurs as a result of the characteristic reaction of the human organism to the effects of certain chemicals (e.g., varnishes, various chemicals, industrial vapors, paints and many more). Information about toxic conjunctivitis of endogenous origin, which occurs due to damage to the eye by bacterial toxins (in the presence of foci of chronic bacterial infection in the kidneys), is not found in the available medical literature.

Under our observation there were 211/2340 (9%) adults and 18/870 (2%) schoolchildren with CBIS who had conjunctival lesions of toxic endogenous origin. Conjunctivitis had no purulent character, and the viral nature of their occurrence was also excluded in the laboratory examination. We mentioned above, when considering the clinical manifestations of dermatotropic toxins, that more than half of adults (1334/2340 or 57%) and even 70/870 (or 8%) of schoolchildren noted such clinical symptoms of toxic irritation of the mucous membranes of the eyes as a constant and sometimes paroxysmal feeling of burning and "sand" in the eyes, that caused moderate or insurmountable tearing. In cases of progression of toxic lesions of the mucous membranes of the eyes there was toxic conjunctivitis (usually there were affected both eyes) with swelling of the eyelids, swelling and redness of the conjunctiva, photophobia, further increased tearing, redness of the whites of the eyes, itchy eyes and sometimes pain in eyes.

Among uveitis (inflammation of the vascular membrane of the eye) the infectious nature of their occurrence is more often wide spreaded, namely – of viral etiology. Both eyes are usually affected. Among the most common are herpes viruses: cytomegalovirus, Epstein-Barr virus, herpes simplex virus and only sometimes - chickenpox virus. Apart from herpes viruses, uveitis can be caused by toxoplasmosis, tuberculosis; in rarer single cases lesions of the visual tract can be at histoplasmosis, toxocariasis, Lyme disease (borreliosis), syphilis and as casuistry - in some other infectious diseases.

In some no single cases, it is impossible to establish the infectious or other known classical nature of uveitis (autoimmune, post-traumatic etc.) - the results of adequate laboratory examination give negative results. As it was determined, usually such uveitis have toxic nature (endotoxic uveitis) and occur due to endogenous damage to the vessels of the uveal tract by toxins of bacteria, whose chronic focus is in the kidneys. A part of these toxins have a corresponding ophthalmotropicity with selective dominance of lesions of the visual tract vessels.

Under our observation there were 24/4500 (0.53%) patients with CBIS who had the previously diagnosed uveitis of unknown etiology. There were 3/750 (0.4%) children aged 3 to 7 years, 7/870 (0.8%) aged 7 to 14 years and 14/2340 (0.6%) adults. More often there were affected both eyes (in 19/24 or 79.2% patients) and almost in all cases (23/24 or 95.8%) it was posterior uveitis with lesions of the choroid, retina and/or optic nerve, including in 3 adults - with a predominance of stagnant discs of optic nerves. Although, perhaps, such selectivity of the lesion was due to the selectivity of the examined patients (only those who went to the infectionist in the clinic) and the limited number of observations of patients with uveal tract lesions. Another 5/2340 (0.57%) adults who were diagnosed with CBIS in our clinic, went with the diagnose retrobulbar neuritis (or neuritis II of the cranial optic nerve with an intact nipple of the nerve). In patients during the previous ophthalmological observations there were excluded demyelinating diseases of the CNS, brain tumors, inflammation of the orbit, sinusitis and other known etiological factors of this rather rare pathological state, the frequency of which is estimated according to various reports from 1 to 5 cases per 100 thousand. Pathogenesis of the optic nerve neuritis remains largely unidentified, although since the 2000s more often some say about the axon and neuron destruction as primary factors in the development of the process, but the cause of this neurodegenerative damage is still unclear.

The duration of diseases, the etiology of which remained uncertain throughout the previous observations, ranged from 5-6 months to 7-8 years. Despite constant professional treatment according to the existing international protocols for such cases, the state of the eyes noticeably and steadily did not improve, and visual acuity constantly declined, as in the following example.

Example 11

Patient T., 18 years old, went to the clinic together with the father, who took care of the daughter as a small child, on September 10, 2014 with a diagnosis of the referral for examination: stagnant discs of optic nerves of both eyes with decreased vision (VOD - 0.4; VOS - 0.3). Previous courses of conventional in such cases treatment, which were carried out in several ophthalmological clinics

in Kyiv, lasted 2 years and 9 months with almost zero results - congestion only intensified, and visual acuity declined. The etiology of these stagnant discs remained unverified. She underwent an additional examination for herpesvirus infections in the clinic - no active forms were found; the state of immunity and rheumatic tests - the norm; there were no serological signs of autoimmune-systemic diseases. At first there was suspected and afterwards confirmed during the bacteriological examination of urine with isolation of 3 urine cultures of Enterococcus faecalis the diagnosis of urogenital dysbacteriosis with the debut of cystitis in the nearest anamnesis (in March 2014) and with the development of nephrodisbacteriosis which proceeded with manifestations of CBIS and, according to the diagnostic system Toxicon, with endotoxicosis, toxemia of the moderate grade of resorptive genesis, as well as with secondary hypochromic anemia, episodes of cephalgia and predominant asthenovegetative symptomatics. Thus for the first time in our practice there was established that congestive discs of optic nerves, loss of visual acuity, as well as changes in MRI and in vasogram of cerebral vessels may have a toxic etiology associated with endotoxicosis of bacterial origin.

There was carried out the first course of treatment with bacterial autovaccine with the addition of 3 autostrains of Enterococcus faecalis with 10 subcutaneous injections. She came for a follow-up examination in 2 months after the end of vaccination (15.12.2014). It turned out that in 15 days after the start of treatment the visual acuity increased almost to normal - 90-100% and completely disappeared visual signs of edema of the optic nerve disc of the left eye, and then in 2.5 months after the start of treatment - and the right eye. Moreover, according to the ultrasound examination of the cerebral vessels, during 2.5 months completely restored symmetrical blood flow through the middle cerebral arteries and there was noted a positive trend in impaired venous outflow from the cranial cavity. In 3 months after the end of the 1st course there were carried out more additionally two courses of vaccination. Initially the 2nd course of immunization with Escherichia coli + enterococcal autovaccine, now with the addition of 3 new autostrains of Enterococcus faecalis and 2 autostrains - *E.coli*, which were isolated during the control examination of warm urine - also with 10 injections, and then more additionally the 3rd course – with bacterial autovaccine, made from autostrains of bacteria, also with 10 injections. During the next 6 years of the follow-up observation there were no recurrences of vision loss (100%-vision in both eyes is preserved), as well as there were no cystitis and bacteriuria.

In 7/2340 (0.3%) adults without manifestation of uveitis and/or optic nerve neuritis developed temporary transient diplopia, which clearly had toxic character, but the mechanism of diplopia remained unclear. It is possible that, as with botulism, there was a toxic lesion of the nuclei III, IV and VI (diversion) of the cranial nerves, but unlike botulinum toxin, the action of bacterial toxins in nephrodisbacteriosis/pyelonephritis had reversible character and disappeared after reducing endotoxicosis, which caused CBIS. It can be assumed that at CBIS there is also not only an established toxic lesion of II (visual) or V (trigeminal) cranial nerves or possible damage to III (oculomotor), IV (block) and VI (withdrawal), but also other cranial nerves, for example, X (wandering) or I (olfactory) nerves with the appearance of the appropriate clinical symptomatics. Moreover that

from the large clinical list of autonomic neuropathies at CBIS, which were considered as peripheral due to the effects of neurovasotropic toxins and were noticed in the vast majority of adults (from 65% to 94%) and often in schoolchildren, a certain part of them could have just the central origin (e.g., heart rate, secretion of endocrine glands). Complaints of olfactory disorders from patients with CBIS have been heard many times, although the reason for their occurrence remained unclear. But this question needs a separate additional study.

At the end of the discussion about the clinical manifestations of CBIS it is necessary to pause on another interesting and important circumstance. In almost 100% of children and in 50-70% of adults with CBIS there was found out chronic staphylococcal infection, the primary focus of which was in the nasopharynx. This introduced into the clinical picture of the disease such typical for this infection clinical symptoms as predisposition to frequent colds, chronic tonsillitis with recurrent sore throats, pharyngitis with frequent pain in throat, inflammatory processes in the paranasal sinuses, ears, eyes, adenoids in children and gradual development of cysts and polyps more often of the maxillary sinus in adults on the background of chronic inflammation of the mucous membranes of the paranasal sinuses, enlargement and soreness of the lymph nodes of the lymphopharyngeal ring, "teenagers" pyoderma, boils etc. Just by the focus of chronic staphylococcal infection in the nasopharynx could be explained such symptoms as pharyngitis, sore throat and enlargement of lymph nodes of the nasopharyngeal ring, which were often referred to earlier while investigating the clinical picture of CFS, but whose appearance remained unknown.

Separately it should also be noted that the development of CBIS did not depend on the presence of an inflammatory process in the kidneys. Thus among 2340 adults diagnosed with nephrodisbacteriosis with the development of CBIS, only 281/2340 (12%) patients had clinical mentions and laboratory and ultrasound confirmation of pyelonephritis at the time of visit to our clinic, and among 2160 children - 173 (8%). Meanwhile in 585/2340 (25%) adults and 411/2160 (19%) children, despite the lack of any data from their anamnesis and clinical manifestations of chronic pyelonephritis, in general urine tests there were detected for the first time microscopic signs of latent formation of chronic delayed inflammatory process in the kidneys with varying levels of protein increase, leukocytes, the appearance of cylinders and bacteria, rarely - erythrocytes. That is 63% of adult patients and 73% of children, at the time of diagnosis of CBIS, had nephrodisbacteriosis in "pure" form without any signs of the inflammatory process in the kidneys.

In a result of the follow-up observation of 700 patients (adults - 420, children - 280) with the diagnosis of nephrodisbacteriosis, who either did not pass at all, or received only 1-2 courses of treatment with bacterial autovaccines, without achieving complete sanitation of the focus in the kidneys, there was found out the following. More than in a third of cases (157/420 or 37.4% of adults and 110/280 or 39.2% of children) there was the debut of pyelonephritis within from a few hours (casuistic cases) to several years (sometimes 8-10 years) after initial clinical establishment and/or bacteriological confirmation of their diagnosis of nephrodisbacteriosis.

Taking this into account, it must be probably admitted that "acute pyelonephritis" almost at all

do not exist. In cases of "acute" inflammation in the kidneys mostly always (except for primary hematogenous lesion of kidneys in septic patients) there is a primary debut of chronic delayed pyelonephritis with usually long-term latent formation on the background of nephrodisbacteriosis. That is at first there is a clinically asymptomatic settlement of the kidneys in ascending path mainly with bacteria of the intestinal group, with enterococci and staphylococci. Such a quiet long-term microbial creeping occupation of the mucous membranes mainly of the cup-bowl and tubular system of the kidneys with the development of distant symptoms of general intoxication (CBIS) at first, and then due to the effect of various adverse trigger factors – the appearance of signs of local inflammatory process, i.e. classical pyelonephritis. One of the frequent provoking factors of the development of nephrodisbacteriosis in adults was urolithiasis. Almost 39% (912/2340) of adults and almost 35% (755/2160) of children, at the moment of visiting our clinic for consultation or from anamnesis mentions about previous episodes of cystitis, had clinical signs of chronic cystitis, which was considered as an additional gateway for an ascending infection.

Despite the large number of symptoms, with which could pass CBIS, in some cases it was possible to say about monosymptomatic CBIS, which had not simply a dominant, but almost only one manifestation: either only a headache, or trigeminitis or reactive arthritis, or alopecia, or prolonged subfebrile, or isolated increased ESR or leukopenia or many others "or". This characteristic circumstance must have been taken into account when examining patients with this clinically variegated CBIS.

The Implications/Conclusions

1. One of the main clinical manifestations of the action of dermatotropic toxins in patients with CBIS was a very frequent direct skin lesion with the appearance of various variants of dermatitis, which, despite the different names, combined one common pathogenetic cause: they were caused by bacterial toxins of dermatological orientation. Bacterial toxicodermas were more often observed in children: in the age under 3 years - in 222/540 (41%) cases, in the age from 3 to 7 years - in 398/750 (53%), from 7 to 14 years - in 392/870 (45%) and in 889/2340 (38%) adults. Skin lesions were almost always combined with other symptoms of CBIS, although skin lesions often markedly dominated in the clinical picture of the disease.

2. Clinical dermatological diagnoses, being established for patients with CBIS, included such more often nosologically separated diseases as actually toxicoderma (in particular, spotted, papular, vesicular, pustular, bullous), atopic dermatitis and other variants of dermatitis (including neurodermatitis, allergic dermatitis, seborrheic dermatitis), erythema (migrating, annular-like, multi-form exudative), urticaria, local asymmetric Quincke's edema usually on the face (lips, eyelids), eczema, psoriasis. That is all these diagnostically stable diseases were considered as different clinical variants of bacterial toxicoderma, which emerged on the background of nephrodisbacteriosis/pyelonephritis and was only one of the manifestations of CBIS, that allowed to change the strategy and tactics of their treatment. Namely: there was treated no skin and allergies, but CBIS, which

led to damage to various organs and systems of the organism, including the skin, that allowed to achieve the effective treatment of bacterial toxicoderma in children, including such diseases as atopic dermatitis and eczema, at the level 80-100%.

3. Clinical manifestations of CBIS, caused by arthromyotropic toxins, included reactive arthritis (ReA), which were observed in 770/4500 (17.1%) patients with CBIS. There were 540/2340 (23%) adults, 157/870 (18%) schoolchildren and 73/750 (9.7%) children aged from 3 to 7 years. According to our observations and the results of treatment of patients with a dominant in the clinical picture of disease reactive inflammation of the joints, this pathological state was not connected with previous acute intestinal and sexually transmitted infections, as well as with chronic genital chlamydia, which are still considered as a major cause of ReA. Moreover it was also found out that ReA on the background of CBIS is present even among sick children and adults with such diagnoses as rheumatoid arthritis, RA (under our supervision there were 70/770 or 9.1% of such patients, including juvenile RA in 9 children or 1, 1%), as well as gouty arthritis - 45/770 (5.8%) cases, psoriatic arthritis - 15/770 (1.9%) and joint damage, which occurred as if on the background of borreliosis (Lyme disease) - in 10 patients (1.3%) that totally made up also 9.1% (70/770). In all these cases ReA developed on the background of a chronic bacterial infection in the kidneys - nephrodisbacteriosis, rarely – of manifest pyelonephritis that has led to the development of CBIS with dominant joint lesions, which were mistakenly diagnosed by other diagnoses.

4. A part of the bacterial toxins at CBIS had another specific clinical direction of action, which was described as ophthalmotropic. Under our supervision there were 211/2340 (9%) adults and 18/870 (2%) schoolchildren with CBIS who had toxic conjunctivitis of endogenous origin with eyelids edema, with edema and hyperemia of conjunctiva, photophobia, lacrimation, redness of the whites of the eyes, itchy eyes, and sometimes - with pain in the eyes.

5. Bacterial toxins at CBIS could cause not only damage to the conjunctiva but also to the visual tract. Under our supervision there were 24/4500 (0.53%) patients with CBIS, which were diagnosed, after the exclusion of viral, bacterial, autoimmune and other nature of the disease, with toxic uveitis of endogenous origin. There were 3/750 (0.4%) children aged 3 to 7 years, 7/870 (0.8%) aged 7 to 14 years and 14/2340 (0.6%) adults. More often there were affected both eyes (in 19/24 or 79.2% of patients) and in almost all cases (23/24 or 95.8%) it was posterior uveitis with lesions of the choroid, retina and/or visual nerve, including in 3 adults - with a predominance of stagnant discs of visual nerves.

6. Other single manifestations of the action of bacterial toxins of ophthalmotropic direction included retrobulbar neuritis of the visual nerve, which was observed in 5/2340 (0.57%) adults, in which during previous ophthalmological observations there were excluded demyelinating diseases of the CNS, brain tumors, inflammation of the contents of the orbit, sinusitis and other known etiological factors of this rather rare pathological state, and temporary transient diplopia, which was observed in 7/2340 (0.3%) adults without manifestations of uveitis and/or neuritis of the visual nerve. The mechanism of emergence of this diplopia, except that it had toxic character, remained

unclear.

7. In almost 100% of children and in 50-70% of adults with CBIS there was found out chronic staphylococcal infection, the primary focus of which was in the nasopharynx. This introduced into the clinical picture of the disease such typical for this infection additional clinical symptoms as predisposition to frequent colds, chronic tonsillitis with recurrent angina, pharyngitis with frequent pain in throat, inflammatory processes in the paranasal sinuses, ears, eyes, adenoids in children and gradual development in adults cysts and polyps more often of the maxillary sinus on the background of chronic inflammation of the mucous membranes of the paranasal sinuses, enlargement and soreness of the lymph nodes of the lymphopharyngeal ring, "teenagers'" pyoderma, boils and others. Just by the focus of chronic staphylococcal infection in the nasopharynx could be explained the appearance of such symptoms as pharyngitis, sore throat and enlargement of lymph nodes of the nasopharyngeal ring, which there were often referred to earlier when studying the clinical picture of CFS, but their emergence remained unknown.

8. The development of CBIS did not depend on the presence of an inflammatory process in the kidneys. Among 2340 adults diagnosed with nephrodisbacteriosis with the development of CBIS, only 281 (12%) patients had clinical mentions and laboratory and ultrasound confirmation of pyelonephritis at the time of visit to the clinic, and among 2160 children - 173 (8%). Meanwhile in 585/2340 (25%) adults and 411/2160 (19%) children, despite the lack of any data from their anamnesis and of clinical manifestations of chronic pyelonephritis, in general urine analyzes there were detected for the first time microscopic signs of latent formation of chronic delayed inflammatory process in the kidneys with varying elevated levels of protein, leukocytes, the appearance of cylinders and bacteria, rarer - erythrocytes. Thus 63% of adult patients and 73% of children at the moment of diagnosing CBIS had nephrodisbacteriosis in "pure" form without any signs of inflammatory process in the kidneys.

9. There was established smuch a characteristic clinical circumstance as the existence of monosymptomatic CBIS, which had not simply a dominant, but almost only one manifestation: or only headache, or trigeminitis, or reactive arthritis, or alopecia, or prolonged subfebrile, or separately elevated ESR (syndrome of separate elevation of ESR), or leukopenia and many other similar "or" that must be taken into account when diagnosing this clinically variegated syndrome.

Report 6: Clinical Diagnosis

Abstract

Objective: of the research was to study the features of clinical manifestations of CBIS in preschool children and teenagers, as well as to analyze the results of laboratory (clinical-diagnostic, biochemical, enzyme-linked immunosorbent assay and PCR, immunological) examination of patients with CBIS.

Design: of the research was as previously clinical-diagnostic and included the determination of clinical manifestations and features of laboratory examination of such a still unknown disease,

which was called chronic bacterial intoxication syndrome (CBIS), which has long been under the mask of a diagnosis of ME/CFS. The studies were prospective-retrospective and were longitudinal. The effectiveness of the obtained results of the study had direct character, because they undoubtedly led to the improvement of the patient's state and life.

The style of presentation of the material is narrative, not tedious. Conditions: the researches were multicenter and conducted in ambulant conditions on the basis of 2 clinics specialized in the field of chronic infectious diseases with a full range of laboratory researches.

Participants: all patients who seeked advice in clinics during 2009-2020 with complaints consistent with a diagnosis of CFS, which was previously diagnosed in almost a third of patients on former stages of examination and treatment.

Results: There have been identified some clinical features of nephrodisbacteriosis and CBIS in children of different ages. It was found out that changes in peripheral blood at CBIS had no specific, but quite typical character with almost constant (in 90-95% of cases) lymphocytosis with the appropriate development of secondary neutropenia, with decreased hemoglobin and erythrocytes (40-50% of cases), with almost stable decrease (25-30% of cases) of leukocytes levels and in 10-15% - platelets, as well as increase of ESR, sometimes - with completely normal other indicators of the general blood analysis. This phenomenon was called the syndrome of isolated increase in ESR. It was found out that the increase of Antistreptolysin O (ASLO) in 58.7% of sick children and adults with reactive and rheumatoid arthritis -, on the basis of which for 90.5% of them there were prescribed antibiotics, and in 85/370 or 23% of cases to "eliminate the focus of streptococcal infection" there was additionally carried out tonsillectomy - was not connected with the streptococcal infection. In 322/370 (87%) patients with joint damage and elevated levels of ASLO during bacteriological examination from the urine there were isolated Enterococcus faecalis (in single cases - other enterococci of this genus), which were previously classified as group D streptococci. While establishing the immune status in patients with CBIS there was found out that their cellular immunity was usually either within normal limits or even more often exceeded normal. Only 65/2160 (3%) children and 445/2340 (19%) adults had minor cellular immune deficiency. On the basis of the results of the study of nephrodisbacteriosis and CBIS, diagnosed for the first time, there were made clinical conclusions.

The known: existence of a diagnosis ME/CFS with an unknown etiological cause.

The new: for the first time it's clinically determined and laboratory confirmed that under the mask of ME/CFS is hidden still unknown chronic bacterial intoxication syndrome (CBIS), which develops on the background of inflammatory focus of chronic bacterial usually locally asymptomatic infection in kidneys, called nephrodisbacteriosis. For the first time there was found out the existence of the syndrome of isolated increase of ESR and for the first time it was proved that elevated ASLO levels may be associated not with streptococcal but with enterococcal infection.

The implications/Conclusions: The clinical course of nephrodisbacteriosis and CBIS in preschool children and teenagers had its own characteristics that had to be taken into account when diagnosing their disease. There were established nonspecific but typical changes in the general blood analysis of patients with CBIS, features of the immune response and there were analyzed the results of ELISA- and PCR-examination for all herpes viruses (HSV 1/2, VZV, EBV, CMV, HHV-6, HHV-7, HHV-8), which clearly proved the absence of any case of herpetic etiology of this pathological state. It has been highlighted the existence of the syndrome of isolated increase of ESR in patients with CBIS and for the first time it was proved that elevated ASLO levels may be associated with nephrodisbacteriosis caused by enterococci.

Key words: chronic bacterial intoxication syndrome (CBIS), nephrodisbacteriosis, syndrome of isolated increase of ESR, Antistreptolysin O (ASLO), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

It should be noted some features of nephrodisbacteriosis and CBIS in children. Nephrodisbacteriosis with minimal clinical manifestations was detected in 50-70% of clinically healthy children during their examination in the clinic before routine vaccination, which included urine cultures examinations of warm urine three times. However the parents did not complain about the child's state and only during their active questionning there was found out that the child sweats a lot when falling asleep, subfebrile temperature can sometimes "run", and in the general blood analysis could be detected a decrease in levels of hemoglobin and erythrocytes.

The clinical palette of CBIS in children of ealier and preschool age was generally much more limited than in adults, but perhaps more pronounced. The first thing that caught an attention was the child's appearance: pale face, dark circles and sometimes puffiness under the eyes, some nervousness or on the contrary indifference in the eyes, noticeable muscle weakness, when the child during the consultation as if simply slipped from a chair. One of the main symptoms was a violation of temperature regime of organism: 45%-65% of children with CBIS (depending on age) had a constant or variable sub febrile temperature, and a third of children (29%-38%) had febrile attacks, which passed under different misdiagnosis. In these cases the temperature in a seemingly healthy child, who just before had run and played uncontrollably, critically fast reached 39-40°C and was clinically almost monosymptomatic (without obvious catarrhal symptoms and signs of any local lesions). As the mother of the boy Andrew, 9 years old, said that is "a sudden temperature". This temperature usually poorly responded to antipyretic drugs and almost did not react to the use of antibiotics that is understandable - because it had no inflammatory but toxic character, and usually lasting from 1-2 to 5-7 days, disappeared. We have said before about such a temperature in children that it came without a declaration of war and leaved without a declaration of capitulation, and it could be also said that it came from nowhere and went nowhere.

Among children who could already formulate their complaints, 113/750 or 15% in the ages from 3 to 7 years and 270/870 (31%) schoolchildren complained of joint pain, and younger children simply stopped to stand up on legs and/or refused to come down from the parents' hands. In almost half

of the cases (from 41% to 53%) there were noted bacterial toxicodermas with different intensity of lesions: from mild skin roughness to severe lesions by the type of the widespread atopic dermatitis and wet eczema with entire skin lesions, when almost no virgin areas remained. In many children with CBIS (37% to 54%) there was noticable increased sweating: in infants and the first 3-5 years of life there was more often increased night sweating, especially when falling asleep, when the underwear, according to the mother, "could be twisted" and had to be changed several times during a night. In children of all ages (7% to 25%) one of the main manifestations of CBIS could be a prolonged reflex cough, usually paroxysmal and pertussis-like cough, which was not connected with inflammatory processes in the nasopharynx and/or in the breathing tract, and had a toxic origin due to irritation of the mucous membrane of the posterior wall of the pharynx and trachea by bacterial toxins.

Among children of different age groups, a typical manifestation of CBIS were various delays of development-body weight gain, speech, mental disorders, emotional disorders and behavioral disorders, which were observed in 25% of children under 3 years, in 17% - from 3 up to 7 years and in 9% of schoolchildren. Herewith the beginning of developmental delays of a child's or their progression was often noted after routine prophylactic vaccinations due to the activation in the nearest post-vaccination period of an asymptomatic focus of chronic bacterial infection in the kidneys, i.e. nephrodisbacteriosis, which was provoked by the vaccination itself. Some parents called such nearest post-vaccination reactions that occurred to their children, "rollbacks" in development. Therefore we consider the presence of nephrodisbacteriosis as a temporary but absolute contraindication for routine vaccinations in children aged less than 3-5 years and do not carry out routine vaccinations without prior tree fold bacterial examination of warm urine. To emotional and behavioral disorders there was included hyper excitability syndrome or the state "hyperactive child". This state could be also called the "monkey" syndrome, when the child cannot be calmed, restrained, persuaded, even forced, as some say "reach out to them": a child will however do what it wants and considers for necessary without even listening to what it is told.

For teenagers there were more appropriate such manifestations of CBIS as increased fatigue, memory impairment, decreased tolerance to sports and mental loading, because of those children began to lag behind the school curriculum and lost interest in sports. Most often at this age there could be a debilitating and severe almost constant headache that responded difficult to treatment with medication and could become the main complaint of the child and its parents, forcing them to wander for months and even years between doctors and to do many useless MRI and CT scans of the brain to answer what is it in general and what happens to their child. Sometimes teenagers noticed muscle weakness (2%), sometimes - local convulsions and twitching (4%) more often in the extremities by type of muscle fibrillation. Sweating in teenagers with CBIS (54%) had its own characteristics: more often it was daytime, could be from moderate to profuse, sometimes with a sharp unpleasant odor of sweat, which parents themselves mistakenly explained that their child "grows up" too early, that it is "age manifestations" and they will soon fade away.

Generally-Clinical Diagnostics

Changes in peripheral blood at CBIS had no specific, but quite typical character. Most often, in almost 90-95% of cases, there was detected relative and absolute lymphocytosis - from moderate to real increase of lymphocytes in 2-2.5 times over the norm, that is usually explained to the patient by "past viral infection", and sometimes there was detected the presence of a small number of atypical mononuclear cells (usually up to 5%). It was also quite typical more often a stable decrease in hemoglobin and erythrocytes (in 40-50% of cases), which in children and adults could last for years, despite not single intensive modern treatment of anemia. Another manifestation of the effect of chronic intoxication on hematopoiesis was an almost stable decrease of leukocyte levels in 25-30% of cases and in 10-15% - of platelets, herewith sometimes leukopenia with neutropenia and thrombocytopenia could be significant pronounced and could reach almost critical levels. No single prescribing in such cases of the most modern drugs to improve leukopoiesis and thrombocytopoiesis usually gave a temporary and limited result. Another manifestation of the impact of chronic intoxication on the general blood analysis was an increase in ESR: from 20-25mm/h to 50-60mm/h, which could also last for years. At the same time other indicators of the blood analysis could remain within norm. This phenomenon has been called the syndrome of isolated increase in ESR, when additional numerous laboratory and instrumental examinations, including for cancer diseases, do not answer the question of where that increased ESR came from. In these cases, as a rule, the general urine analysis and ultrasound diagnostics of kidneys do not reveal pathology. And only bacterial examination of urine with isolation of urinary cultures of bacteria and subsequent treatment with appropriate bacterial vaccines made it possible to clarify this diagnostically indeterminate situation and to reduce and even to normalize ESR.

Neutropenia at CBIS almost always had secondary dependent character and usually was the result of primary lymphocytosis, which in its turn most likely occurred in response to the formation of a focus of chronic bacterial infection in the kidneys (nephrodisbacteriosis). Therefore very often lymphocytosis was detected simultaneously with the left-side shift in the blood formula. The immune system as if "feels" the presence of infection, but in the antigenic plan does not fully recognize it. Therefore it increases the circulation of lymphocytes in the peripheral blood that can be conditionally considered as a compensatory reaction of the cellular link of immunity in order to enhance the effectiveness of the immune response to bacterial antigens. At the same time the level of lymphocytes (at the upper limit of norm in adults and children after 5 years in 37%) could increase up to 50%, 60% and sometimes even to 70-75% that often became a reason to consult a hematologist. And taking into account the simply catastrophically secondary low level of granulocytes (up to 150-100 cells/μl, possibly lower), because the total number of cellular elements in the blood formula, as it's well known, should be 100%, such patients with CBIS not in single cases even underwent the bone marrow puncture, which, unfortunately, did not add anything new in terms of differential diagnosis. Despite the long-term specific hematological treatment, restoration of the balance of granulocytes and lymphocytes in patients with CBIS was almost impossible to

achieve by prescribing granulocyte-macrophage colony-stimulating drugs. The following clinical example confirms such observations.

Example 1.

Child B, 18 years old, was consulted in absentia in connection with severe movement disorders (bedridden invalid): spastic cerebral palsy, tetraparesis, symptomatic epilepsy (from 1 year 8 months). Congenital bilateral cataract. Cyst of the right kidney. In the neonatal period and in infancy he suffered from pathological jaundice, osteomyelitis of the femur, purulent arthritis of the hip joint, severe meningitis. Subsequently he had at least 10 pneumonias with the development of pneumofibrosis. Almost constantly, among other treatments, he received antibiotics. The child is observed and treated at the Orphan Diseases Center. During the past 4-5 years developed stable pronounced leukopenia (1.5-2.2x10^9/l), persistent lymphocytosis (up to 57%), secondary neutropenia (up to 150-350 cells/μl), anemia and thrombocytopenia of unknown etiology. From March 28, 2018 during 1.5 years, he almost constantly received G-CSF (granulocyte-macrophage colony-stimulating factor) and other drugs that stimulated granulocytopoiesis, at the beginning three times and then 5 times a week. This treatment proved to be almost ineffective: leukopenia and granulocytopenia returned quickly or persisted at a minimum low almost critical level on the background of persistent lymphocytosis.

The boy's mother went to the clinic for a consultation on November 27, 2019. The examination (analyzes were collected at home) revealed chronic CMV- and EBV-infections (in the latent and low-active replicative stages, respectively), *St.aureus* and *Str.pyogenes* in the nose and throat, one strain of Klebsiella pneumoniae in urine. There was diagnosed nephrodisbacteriosis (predominantly Klebsiella) with recurrent episodes of proteinuria, leukocyturia, erythrocyturia and bacteriuria in the anamnesis (since 2014) and at the moment of consultation with the development of CBIS with a predominant persistent sub febrile and hematological manifestations as well as the chronic staphylococcal infection. Chronic CMV-infection was most likely considered as congenital with a predominant CNS lesion and a trigger factor of the development of early secondary bacterial infections, and purulent-inflammatory processes in infancy and later in the anamnesis - as manifestations of chronic staphylococcal infection. There was prescribed the first cycle of treatment with bacterial vaccines, which consisted of 3 courses for 3.5 months: first - monovalent staphylococcal auto vaccine No.7, then - divalent Klebsiella-staphylococcal auto vaccine No.10, and then - revaccination with staphylococcal vaccine No.5. At the follow-up examination immediately after the end of the 3rd course of vaccination in March 2020, the level of leukocytes increased from 1.62x10^9/l to 3.56x10^9/l, and the level of neutrophils - 10 times from 150 cells/μl to 1500 cells/μl. In June 2020 due to the isolation of 3 strains of Citrobacter freundii from warm urine during the control bacterial examination and taking into account the partial reduction of these indicators, there was prescribed a second cycle of treatment with appropriate bacterial autovaccines. Granulocyte colony-stimulating factors since December 2019 (after the start of vaccines usage) he did not receive anymore. Here is what the mother of this guy wrote to me on April 13, 2020, direct speech: “I want to share my joy. ... Now we have completed the third stage of treatment and passed

the control blood analysis. Now our leukocytes are 3.54!!! And when we went to you there were 1.6. Total neutrophils 1.5!!! And there were 0.15. There is no need to crack this expensive and already inefficient Philstim!!! Thank you very much!!! Everyone is sad about the coronavirus, and I dance Lezginka with happiness. Thanks!"

In general urine analyzes, as mentioned earlier, in 25% of adults and 19% of children, despite the absence of any anamnestic and clinical mentions and manifestations of chronic pyelonephritis, there were detected for the first time microscopic signs of latent formation of chronic delayed inflammatory process in the kidneys with different increased levels of protein, leukocytes, the appearance of cylinders and bacteria, rarely - erythrocytes. Sometimes the microscopic changes in the general urine analysis for a long time had so insignificant character that neither the doctor nor the patient himself even paid attention to them. But at the same time in 63% of adult patients and 73% of children at the moment of CBIS diagnosing their general urine analysis did not show any manifestations of inflammatory process in the kidneys and remained almost perfect. That only confirmed the existence of such a diagnosis as nephrodisbacteriosis, on the background of which there was the development of CBIS.

Biochemical blood examinations did not reveal any significant changes and abnormalities inherent for CBIS. But one circumstance still attracted attention and required interpretation. In more than half of the sick children and adults with reactive and rheumatoid arthritis during their examination on rheumatic tests there were detected elevated levels of antistreptolysin O (ASLO), at the same time rheumatoid factor and C-reactive protein usually remained normal. The level of increase was often significant and ranged from 250-300 up to 1500 IU/ml. It is well known that antistreptolysin O is an antibody which is synthesized by the human organism against one of the streptococcus antigens, namely against hemolytic exotoxin, which is secreted by most streptococci strains of group A and many strains of groups C and G. Therefore it is clear that the detection of ASLO is interpreted as confirmation of the streptococcal infection and evidence of the etiological role of streptococcus in the occurrence of a certain list of diseases, which include joint lesions. Blood analysis for ASLO are used not only to confirm streptococcal infection, but also to monitor the course of its treatment (with recovery, indicators decrease). And streptococcal infection is treated, of course, with antibiotics. Moreover, if a patient with joint damage and elevated ASLO also has chronic tonsillitis, and the results of antibiotic treatment are disappointing, it is clear that without the removal of the tonsils, the disease cannot be defeated.

During the last 11 years (since 2009) under our supervision and treatment there were 770/4500 (17.1%) patients with CBIS on the background of nephrodisbacteriosis and/or pyelonephritis with a dominant joint lesions in the clinical picture of disease, as it was previously reported in the section arthromyotropic toxins. Among 630 patients diagnosed at previous stages of examination and treatment (reactive arthritis - in 560/770 or 72.7% of cases and rheumatoid arthritis - in 70/770 or 9.1%), an increase of ASLO was detected in 370/630 (58.7%) patients, including 135/370 (36.5%) children and 235/370 (63.5%) adults. Almost for all of these patients (335/370 or 90.5%) there were prescribed antibiotics, usually bicillin intramuscularly in long courses, which patients received from several months to 2-3 years continuously. Moreover, in 85/370 or 23% of cases (children -

53/135 or 39.2%, adults - 32/235 or 13.6%) to "eliminate the focus of streptococcal infection" there was carried out tonsillectomy. Despite the temporary improvement of the state in some cases, no one patient recovered completely, recurrences of joint damage continued and further, and the level of ASLO not only did not decrease, but more often even increased on the contrary. And only after the treatment of CBIS it was possible to stop the recurrences of joint damage and to normalize the indicators of ASLO. As in the following case.

Example 13.

In November 2012, to the clinic went the parents of a 14-years-old boy who live in the regional center almost on the western border of Ukraine. The son was not taken with them to Kyiv, because he could hardly move on his own. He had been suffering from reactive arthritis for 2 years, during which he had been receiving bicillin injections every week for 18 months, but while treating the child had not gotten better but worse and worse. It all started with inflammation of one knee joint, and now there are almost no healthy intact joints. He moves with the help of his parents, because he is ashamed to take crutches. The level of ASLO, which at the beginning of treatment was 570 IU/ml, gradually increased to 1550 IU/ml. After talking to the parents, it became clear that the joint lesions developed 2 years ago on the background of CBIS, some symptoms of which appeared in a boy in preschool age, then they became more, from 10 years began to ache joints, which over 2 years began to become inflamed. The parents took with them home the Diaslides (NovaMed Ltd.) for bacterial examination of warm urine, and in a few days later the father came to Kyiv again and brought them to the clinic for examination. From all 3 portions of warm urine, despite constant injections of bicillin, there were isolated 3 identical cultures of Enterococcus faecalis, from which there was, produced a bacterial monovalent auto vaccine from 15 injections. *St.aureus* was isolated from the nose and pharynx. Antibiotics that were contraindicated for the child were immediately discontinued. During the next 2 months he underwent the first course of vaccination, and in 1 month – additional course with another vaccine, bivalent made from another strain of enterococci (Enterococcus faecalis) and Escherichia coli (*E.coli*), which were isolated during control bacterial examinations in February 2013. Over 6 months after the start of treatment in May 2013, the parents came to the clinic again and again without the boy. They told that their son had no complaints, his joints did not ache and did not get inflamed, he received no longer antibiotics, and the ASLO level dropped to 410 IU/ml. When I asked them where the boy was and why he didn't come to Kyiv himself, the parents were embarrassed and a moment later answered that the son was making up for lost time and from the morning until night… "playing football". So he replied that he had now "nothing to do in Kyiv." So he was probably right. Until 2017 there were no more recurrences of arthritis, and then the connection was completely interrupted. That's good: when a patient forgets about his doctor, it is a good symptom. So he recovered and he no longer needs a doctor.

It should be noted that just Enterococcus faecalis (in single cases - other enterococci), as in the above observation, was isolated in 322/370 (87%) patients with joint lesions and elevated levels of ASLO. Moreover, elevated levels of ASLO were detected also in other patients (with psoriasis, Lyme disease) with joint lesions and even in the absence of signs of involvement in the process of joints in

cases of etiologically dominant enterococcal nephrodisbacteriosis or pyelonephritis.

Taking into account our observations of patients with CBIS with joint damage, it can be stated that an increase in ASLO, despite the name, is not always a sign just of streptococcal infection. This indicator may increase in the presence of a focus of chronic bacterial infection in the kidneys, namely caused by enterococci (most often - Enterococcus faecalis, which is the main symbiotic bacterium of the human intestine of this genus and makes up 90-95%). It's important that until 1984 bacteria of the genus Enterococcus were classified as group D streptococci, so long as it was shown by genomic DNA analysis that it was more correct to place them in a separate genus of the family Enterococcaceae. Therefore it is possible that just due to common antigens between these previously related streptococcal pathogens the ASLO increases not only in patients with streptococcal but also with enterococcal infection.

While determining the immune status of almost all patients with CBIS under observation, there was found out the following. Cellular immunity was usually either within norms or more often even exceeded the norm. Only in 67/2160 (3.1%) children and in 451/2340 (19.3%) adults there was detected the minor cellular deficiency with the selective decrease of T-lymphocytes levels (CD3+, CD19-), T-helperocytes (CD3+, CD4+, CD8-), T-suppressors (CD3+, CD4-, CD8+), natural killers (CD3-, CD56+), cytotoxic cells (CD3+, CD56+) and some others. In 1912/2160 (88.5%) children and 746/2340 (31.9%) adults indicators of cellular immunity even exceeded the norm. Prevailing decrease of natural killers and increase of the level of CIC/CEC (Circulating Immune Complexes), which some researches of immunity at CFS report about, in patients with CBIS there was not detected. Only in 464/2340 (19.8%) adults and 157/2160 (7.3%) children there was found out an increase of CIC mainly due to small- and medium-molecular complexes. Levels of immunoglobulins IgA, IgM and IgG, as well as C3 and C4 complements remained within norm limits almost in all patients.

Cellular immune deficiency in patients with CBIS was considered as secondary and also largely associated with endotoxicosis. Over 3-6 months after starting treatment with bacterial vaccines, the state of the immune response without additional prescribing of immunostimulatory drugs usually improved or even normalized. That is the development of CBIS was not due to poor immunity, which on the contrary - was as if mobilized and very often exceeded the norm. Long-term observation of patients with CBIS and the results of their treatment allow us to make the following clinical assumption.

In cases of chronic bacterial infections emerges a certain immunological tolerance: the immune system "brakes" and does not recognize live bacteria that cause various chronic diseases. Or due to the fact that these bacteria are phylogenetic symbiotes that inhabit the human intestine for life (enterobacteria and enterococci), the antigenic structure of which the immune system ceases to differentiate as "foreign" and does not support it at the general and local levels. Or due to the fact that contamination with these bacteria (staphylococci and streptococci, which are natural and one of the most wide speeded infections of human society) occurs daily and many times since the first days of life that reduces the level of protective immunological barrier and causes peculiar

immunological paralysis of local immunity on mucous membranes and of the general immune response. This leads to a long, often lifelong persistence of bacteria in various organs and systems that is manifested (in the context of existing treatment protocols with the constant use of antibiotics) by clinically incurable diseases. The use of antibiotics only exacerbates the decline of the general and local immunity, enhances the state of immunological tolerance to these bacteria and converts chronic bacterial diseases, which occur as a rule in childhood, into a lifelong problem. Therefore the immunity in patients with CBIS is not bad, it is "blind", because it does not see just those bacteria that live in the human organism lifelong.

The results of ELISA and PCR examination of patients with CBIS for herpes viruses (HSV 1/2, VZV, EBV, CMV, HHV-6, HHV-7, HHV-8) clearly proved the absence of any case of herpetic etiology of this pathological state emergence. The level of chronic HSV type 1 infectioning made up in adults 90-92%, HSV type 2 - 78-80%, the level of post-infection (usually) or post vaccination immunity to VZV - up to 80%, chronic EBV infecting - 98-100%, CMV - 92-94%, HHV-6 - 98-100%. However on the basis of systematic PCR-monitoring, there has not been established any case of evidentiary confirmation of the etiological role of these viruses in the emergence of CBIS-symptoms in 4500 sick children and adults. No patient was prescribed antiviral treatment, and in those cases when it had been already previously prescribed, it was canceled due to its uselessness.

As noted earlier in Report 1, during observations there was proved that up to 25% of children and 20% of adults almost constantly secrete the virus with saliva while remaining clinically healthy. Moreover, it should be once more emphasized that with the constant use of quantitative PCR test-systems in the Markov Clinic for the determination of EBV DNA with a relatively low sensitivity threshold (at a level 500 copies of DNA/ml) very often in patients with a determined very large number of copies of EBV DNA in saliva from the level of 500 thousand to several million (in single cases - more than 50 million copies of DNA/ml) there were completely absent any clinical manifestations of EBV infection. And the positive results of PCR tests in a few weeks, generally without any antiviral treatment, decreased to a small number of copies or even became completely negative.

Bacteriological and toxicological confirmation of the diagnosis will be separately in detail considered in the following Reports 7 and 8.

Clinical Conclusions

The disease CBIS can usually last from 1-2 years to 20-25 years, and probably longer, in direct dependence, to a greater extent, on attempts to "cure" it with antibiotics. It seems that in the absence of antibiotics for children and adults, up to 50% of those who suffer from nephrodisbacteriosis and its derivative CBIS, have a real chance to overcome this pathological state on their own and recover. Attempts to win by "killing" bacteria and antibiotic treatment are doomed to failure, and the disease will never go away on its own. As a rule CBIS has a wavy course, when exacerbations with significant deterioration of the state alternate with relatively good health with a decrease in the

intensity of clinical manifestations or even with periods of their complete disappearance.

Running a little ahead, it should be noted that in the same way the clinical response courses wavy to treatment with bacterial vaccines. The first so long-awaited positive results of treatment may be felt perhaps by some particularly vulnerable patients already within a few days after the first injections of the bacterial auto vaccine. After improvement of the state almost always there is a "rollback" a little, well-being becomes worse. At this moment the most important thing for the patient is not to lose heart. Then after the beginning of the next course the state improves again and then worsens again. Such a clinical swing ("flip-flap") usually characterizes the typical course like just the disease CBIS so and the response of the sick patients to treatment with bacterial vaccines. But with each subsequent course well-being becomes better and better, approaching to the mark of "100% recovery" and already almost never returns during the deterioration to the same zero from which the treatment began.

Probably it is no coincidence that CFS, which was included in the previous ICD-10 (1990), in 2019 due to "lack of sufficient data" was excluded by the WHO from the register ICD-11 of officially identified diseases with the following wording (according to the manager of the WHO Department of Mental Health, Dr. Tarun Dua, double translation into English): "Chronic fatigue syndrome is a state that during the past couple of years has received increased attention and has become a topic of discussions for the new International Classification of Diseases. For the moment being we believe that more information has to be gathered and more research has to be done to clearly understand how chronic fatigue syndrome emerges in people, what is the exact mechanism of the disease and what can be done to prevent it."

Simultaneously with the exclusion of CFS from ICD-10, there was included to ICD-11 such a new diagnosis as burnout syndrome which emerges due to chronic stress in the workplace. That is chronic stress at work can lead to emotional burnout. The main signs of such "burnout" are considered to be loss of energy, a feeling of exhaustion, psychological distancing from work, negative and pessimistic thoughts about work, reduced professional efficiency. We can nothing do with it, but these symptoms are something very reminiscent. Do you remember how CFS was called earlier else - correctly, a disease of systemic intolerance of loading. Whether is the burnout syndrome a kind of compensation of CFS for its exclusion from the ICD? And why, say, out of 10 workers who are satisfied with their work and simply "burn" in the workplace, only some workers "burn out" and other workaholics remain healthy and even a little unburned? Questions remain.

The negative role of antibiotics in the emergence and development of such pathological states as nephrodisbacteriosis and CBIS is evident. Infecting of the urinary organs and pathways with enterobacteria and enterococci is a physiological process and occurs daily in all without exception children and adults, women and men, even under super-ideal and the most stringent sanitary and hygienic conditions. But the emergence and progression of the focus of chronic bacterial infection in the kidneys without exaggeration in every 9 cases out of 10 registered depends on the aggressive and often senseless prescription of antibiotics by doctors. According to our observations, just in

every 9 out of 10 cases the prescription of antibiotics may be unnecessary at all.

Chronic fatigue under the diagnosis CFS can accompany such diseases as multiple sclerosis, Parkinson's disease, motor neuron disease, chronic cerebral ischemia, stroke, post-polio-syndrome and others. Chronic fatigue can emerge over time with any chronic somatic and neurological diseases. And quite often just fatigue there is presented by patients as the main complaint. In CBIS, which is also a clinically motley disease, additionally it may be also denoted as background states the thyroid disease, changes in sex hormone levels, menopause, lactation and breastfeeding periods, prolonged stress etc. But the common cause of such a state of chronic fatigue, as, perhaps, in the above-mentioned previously known cases, regardless of the background disease, may be just nephrodisbacteriosis with the development of endotoxicosis. But this is only an assumption. This question needs further in-depth study. It should be also noted that CFS, as known, there was identified as a heterogeneous disease that is realized by different pathophysiological mechanisms, but manifests with similar symptoms. CBIS, on the contrary, emerges with a single pathophysiological mechanism of chronic endotoxicosis, and clinically is realized by multi-vector toxic lesions of the mucous membranes, skin, separate organs and entire systems of organism.

Summarizing all the above, we must emphasize the following. Chronic fatigue, the name and patronymic of which is now called a nosologically independent disease - chronic fatigue syndrome - is just one of dozens of other symptoms by which this state can be manifested. And each patient has its own dominant complaint: it can be really fatigue, or low-grade fever, or headache, or joint pain and their inflammation, or muscles pain and their stiffness as a manifestation of fibromyalgia, or skin rash, or significantly increased sweating with a sharp and unpleasant body odor, or multivector phobias, or, or, or. Sometimes due to the dominant complaint, such a pathological state gets a nosologically independent name (e.g., trigeminitis, fibromyalgia, atopic dermatitis, alopecia, reactive arthritis etc.) and long-term sometimes lifelong treatment which cannot be cured. The only thing that combines all these selectively dominant complaints and symptoms may be the reason that causes them. And it's not viruses, known or unknown, which researchers are so persistently looking for in such patients, but severe intoxication, or rather - endotoxicosis, which is connected with a focus of chronic bacterial infection in the kidneys. Just in the kidneys, because it is probably the single such silent organ in the human organism, in which bacteria that have settled there and remain locally invisible, without causing inflammation, secrete toxins which are absorbed into the blood with such incredible speed and cause this severe state - chronic bacterial intoxication syndrome (CBIS).

Although it's necessary in advance to agree with the opinion that is likely to arise after reading these lines. The statement that in the basis of chronic fatigue in various diseases there is a single pathogenetic mechanism - persistent chronic bacterial intoxication due to nephrodisbacteriosis may be a little premature. And to emphasize that the chain of events, established by us, is universal and extends to such a large list of existing diseases, at the moment being before conducting other independent research, it is perhaps still too bold and optimistic.

But, perhaps, the time has come to call this independent disease, which for a long time and still remains hidden under completely other diagnoses and syndromes, as it deserves - a chronic bacterial intoxication syndrome (CBIS). That is to call by its own name, not by alien, although related with chronic fatigue syndrome. And if someone, after reading as above,will has a desire to check whether all the above is really happening or it's an illusion, that's good. Simply do your patient with a diagnosis of CFS, which seems to no longer exist today, because it is excluded from the new 2019 international classification of diseases, and with other mentioned diagnoses the bacteriological examination of urine, preferably warm and not less than 3 consecutive days. And then you, like us earlier, can see everything that happens to your patient in another light. A wonderful world of completely different and seemingly unrelated symptoms and syndromes, which was usually combined with the phrase chronic fatigue syndrome, the cause of which, despite a long-term and persistent search, has still remained unknown. But which have the same origin and are caused by severe endotoxicosis, which usually causes a locally asymptomatic focus of chronic bacterial infection in the kidneys. Moreover one of the main reasons for the emergence of such a focus, which, in our opinion, has to be rightly called as nephrodisbacteriosis, which causes further related with its problems in human life, is at the moment being a senseless and aggressive long-term strategy and tactics of the constant prescription and use of antibiotics. And what is especially unfortunate, this occurs according to WHO international protocols. It is difficult even to imagine how many patients in the world today suffer from nephrodisbacteriosis and CBIS after long and no single courses of antibiotics that they usually do not need, without guessing, unfortunately, what is really happening to them. Do it - and you will not regret it.

There are hopes that just these two previously unknown diagnoses - nephrodisbacteriosis and chronic bacterial intoxication syndrome - can answer many clinical questions about the origin and development of various pathological states of unknown etiology and can become for doctors the key to open many still closed diagnostic doors. And for disconcerted patients who for a long time go with the flow and suffer because they cannot be cured, to become just that straw which they can grab to swim out in the ocean of unidentified or etiologically uncertain diagnoses.

We also understand that after the publication of these materials many specialists each in their field - neurologists, psychiatrists, dermatologists, rheumatologists, ophthalmologists, nephrologists and others will attack two infectionists who allowed themselves to invade their kingdoms. Sorry in advance. Sorry for terminology, for uncertain details, for violation of fixed concepts and ideas, for everything that can irritate you, colleagues. But we do not regret, because it was worth that.

The Implications/Conclusions

1. The clinical palette of CBIS in young and preschool children was much more limited than in adults, but perhaps more pronounced and was usually characterized by the appearance of the child (pale face, dark circles and sometimes swelling under the eyes, some nervousness or on the contrary indifference in the eyes, noticeable muscle weakness), by low-grade fever (in 45%-65% of children), a third of children (from 29% to 38%) - febrile attacks, which took place under various

misdiagnosis, joint pain (from 15% to 31%)), in almost half of the cases (from 41% to 53%) – by bacterial toxicoderma, increased sweating (from 37% to 54%), sometimes (from 7% to 25%) – by prolonged usually paroxysmal pertussis-like cough.

2. Among children of different age groups a typical manifestation of CBIS were various developmental delays – body weight gain, speech, mental disorders, emotional disorders and behavioral disorders, which were observed in 25% of children under 3 years, in 17% - from 3 up to 7 years and in 9% of schoolchildren. Emotional and behavioral disorders included hyperexcitability syndrome, when the child could not be restrained, calmed down, persuaded or even forced: however a child did that and so what it wanted and considered for necessary.

3. For teenagers the most common manifestations of CBIS were general asthenia (64%), intoxication shadows under the eyes (68%), increased fatigue (53%), sweating (54%) from moderate to profuse, sometimes with a sharp unpleasant odor of sweat, which mistakenly was considered as puberty manifestation, prolonged low-grade fever (65%) or febrile attacks (29%), memory impairment (39%), headache (32%), sometimes severe, debilitating, almost constant and clinically dominant, decreased concentration and attention (32%), rapid exhaustion (55%), decreased tolerance to sports and mental loads (15%), in connection with which children began to lag behind the school curriculum and lost interest in sports, in a quarter of cases - phobias (25%).

4. Changes in peripheral blood at CBIS had no specific, but quite typical character: in 90-95% of cases there was detected relative and absolute lymphocytosis from moderate to elevated by 2-2.5 times, more often a stable decrease in hemoglobin and erythrocytes levels (in 40-50% of cases), in 25-30% of cases almost stable decrease of leukocyte levels and in 10-15% - platelets; at this time sometimes leukopenia ($1.5\text{-}1.0x10^9$/l) with neutropenia (up to 150-100 cells/μl) and thrombocytopenia could be significantly pronounced and reach almost critical levels that required consultations with hematologists and sometimes led to a bone marrow puncture.

5. Another manifestation of the effect of chronic intoxication on the general blood analysis was an increase in ESR: from 20-25 mm/h to 50-60 mm/h, sometimes even higher, which could also last for years. At the same time other indicators of the blood analysis could remain within norm. This phenomenon was called the syndrome of isolated increase in ESR, when additional numerous laboratory and instrumental examinations, including - for cancer diseases, did not reveal the cause of such an increase. In these cases, as a rule, the general urine analysis and ultrasound diagnostics of kidneys also did not reveal pathology.

6. In more than half of the sick children and adults with reactive and rheumatoid arthritis during their examinations in other clinics for rheumatological tests there was found out the elevated level of antistreptolysin O (ASLO), which was correspondingly interpreted as confirmation of streptococcal infection and evidence of the etiological role of streptococcus in the emergence of joint lesions. Among 630 patients, diagnosed with ReA (in 560/770 or 72.7%) and RA (in 70/770 or 9.1%) on the previous stages of examination and treatment, the ASLO elevation was detected in 370/630 (58,7%)

patients. Almost all of these patients (335/370 or 90.5%) were prescribed antibiotics, which patients received from several months to 2-3 years continuously.

Tonsillectomy, which was additionally carried out in 85/370 or 23% of the sick (children - 53/135 or 39.2%, adults - 32/235 or 13.6%) in order to "eliminate the focus of streptococcal infection", was unnecessary. Despite the temporary improvement of the state in some cases, no one patient after surgery did not recover completely, recurrences of joint damage continued father, and the ASLO level not only did not decrease, but more often on the contrary even continued to increase.

7. It was found out that in 322/370 (87%) patients with joint damage and elevated levels of ASLO from urine during the bacteriological examination there was isolated Enterococcus faecalis (in single cases - other enterococci of this genus), which until 1984 were classified as group D streptococci, and only then they were assigned to a separate genus of the family Enterococcaceae. Therefore it is possible that just due to common antigens between these previously related streptococcal pathogens the ASLO increases not only in patients with streptococcal, but also with enterococcal infection. Moreover elevated levels of ASLO have been more than once detected in other patients (with psoriasis, Lyme disease) with joint lesions and even in the absence of signs of involvement of joints to the process in cases of etiologically dominant enterococcal nephrodisbacteriosis or pyelonephritis.

8. Cellular immunity in patients with CBIS was usually within normal limits. Only 67/2160 (3.1%) children and 451/2340 (19.3%) adults had a slight cellular immune deficiency with a selective decrease of the levels of T-lymphocytes (CD3+, CD19-), T-helpers (CD3+, CD4+, CD8-), T-suppressors (CD3+, CD4-, CD8+), natural killers (CD3-, CD56+), cytotoxic cells (CD3+, CD56+) and some others. Moreover in 1912/2160 (88.5%) children and in 746/2340 (31.9%) adults the indicators of the cellular immunity even exceeded the norm. Secondary immune deficiency with a predominant decrease of natural killers and with an increase of CIC level, which report some researchers of immunity at CFS about, has not been established in patients with CBIS.

Biography

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