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PATHOGENESIS OF A CASCADE MECHANISM OF CHRONIC GASTRODUODENAL DISEASES IN CHILDREN CAUSED BY LOW QUALITY DRINKING CONTAINING HYPERCHLORINATION AND MANGANESE PRODUCTS

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Abstract. The study focuses on pathogenesis of chronic gastroduodenal diseases in children caused by low quality drinking water containing hyperchlorination products (chloroform) and manganese. It was determined that the clinical manifestation of the pathological process in children with a higher level of manganese and chloroform in blood is conjugated with the development of parasympathetic-type vegetative disfunction, reactive changes in the liver tissue, hypomotor-type biliary disfunction, and hyperkinetic-type gastric and duodenal motor activity disorder. Pathogenesis of chronic gastroduodenal diseases in children [Hp^-] associated with the impact of hyperchlorination products (chloroform) and manganese predetermine pathomorphism of the pathologic process with the development of atrophic / preatrophic changes in the mucosa of the upper digestive tract.
Key words: chronic gastroduodenal pathology, children, quality of drinking water, hyperchlorination products, manganese.

Introduction. Chemical contamination of drinking water due to technogenic factors is a major issue leading to the diseases of the digestive system p5, 7. Degenerative and atrophic processes in the gastro or duodenum of children are associated with, among other factors, the negative impact of chemical substances of technogenic nature [2, 3, 6]. At the same time, pathogenesis of chronic gastroduodenal pathologies in children associated with the negative impact of chemicals of technogenic nature requires further research. The presence of residual products of hyperchlorination products and heavy metals causes additional cases of gastroduodenal diseases (18‰ more cases per year), higher incidence of severe and complicated diseases with a relapsing course and resistance to conservative treatment [1, 4, 8].

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The purpose of the research is to study the pathogenesis of chronic gastroduodenal diseases [Hp^-] in children associated with low quality drinking water containing hyperchlorination products and manganese.

Materials and methods. Assessment of the quality of drinking water and atmospheric air in the areas of residence of children conducted on the basis of the monitoring data by the Federal Information Fund of SHM data (under the RF Government Regulation of 02.02.2006 #60 "Regulation on the Social and Hygienic Monitoring" as amended on 04.09.2012).

The assessment of health risks associated with the consumption of low quality drinking water containing hyperchlorination products and manganese was conducted following the standards under "Guidance on the Assessment of Health Risks Associated with Exposure to Environmental Chemicals" (P 2.1.10.1920-04) [9].

Medical and biological studies were conducted in observance with the ethical principles laid out in the Helsinki Declaration (1975, amended in 1983) and following the National Standard RF GOST-R 52379-2005 "Good Clinical Practice" (ICH E6 GCP) (adopted on 27.09.2005).

The observation group was made up of 116 children with chronic gastroduodenal pathologies [Hp^-] (МКБ-10: К29.3-29,9) aged 7-10 (8,6±1,2), residing in the areas with poor quality drinking water in terms of sanitary and chemical indicators (hyperchlorination products, manganese). The comparison group included 56 children with chronic gastroduodenal pathologies [Hp^-] (МКБ-10: К29.3-29,9) of the same age (8,4±1,4, $p \geq 0,05$), residing in the areas with acceptable water quality in terms of hygienic standards. The groups were compatible in terms of gender of the participants.

To confirm the diagnosis, we used fibrogastroduodenoscopy along with the results of a morphohistologic examination of biopsic samples of the gastric and duodenal mucosa. (gastrofibroscope FG-1ZP, Japan) conducted following a standard method; Helic Test (Helic ABT Reader, a computer-based device for instant diagnostics with an indicator for primary infection diagnostics Helicobacter pylori, регистрационное удостоверение №ФС022а2004/1274-05), and enzyme-linked immunosorbent assay to detect antibodies to H. pylori (conventional method with the use of a standard "Vector Best" test-kit).

Chemical analysis of the level of manganese in blood was conducted with the use of atomic absorption spectrophotometry on Aanalist spectrophotometer by PERKIN-ELMER (USA). The level of chloroform was determined with the use of gas chromatography on Chromatec-Crystal-500 chromatograph with the halogen-selective detector.

Clinical, functional and instrumental examinations of children included the following steps: a medical and social survey based on a special questionnaire, analysis of the medical histories (Form #112/u) as well as pediatric, gastroenterologist and neurologist exams.

Assessment of the vegetative nervous system was conducted with the help of “Poli-Spektr” cardiosoftware based on mathematical analysis of the cardio rhythm, on “VNS-Micro” cardiointervalographer, Neurosoft, Russia (registration ID № 98/219-91). Ultrasonic scanning of the liver, gall bladder, bile passages, gastro and duodenum was conducted with the use of a standard method on “Toshiba VIAMO” (Japan), with the help of a curved array (1.9-6.0 MHz) and linear array (7.0-14.0 MHz) multi-frequency transducers. The parameters of the brain cord biorhythms were analyzed with the help “Neuron-Spektr-4/VPM” electroencephalograph (Russia) using a standard “10-20” method.

Laboratory examination included the following: assessment of the oxidation and anti-oxidation processes (general anti-oxidant activity of the blood serum, concentration of malondialdehyde, Cu/Zn- superoxide dismutase, glutathione peroxidase, glutathione-S-transferase, and lipid hydrogen dioxide), factors of nonspecific resistance (absolute phagocytosis, phagocytic index, phagocytic ratio, and phagocytic number), immunological status (absolute and relative content of CD4+, CD25+, CD95+ lymphocytes), non-specific sensitization ($JgE_{общ}$)), hormonal status (level of serotonin, dopamine, cortisol), neurotransmitters that regulate the processes of excitation and inhibition (level of glutamate and gamma-aminobutyric acid) in blood pepsinogen 1 and pepsinogen 2, alkaline phosphatase, alanine aminotransferase and aspartic. The studies were carried out with the help of conventional methods using a microscope “Micros MC-200" (Austria), automatic biochemical analyzer «Konelab» (Finland), enzyme immunoassay analyzer «ELx808» and standard test kits. Immunogenetic research methods (PCR-based diagnostics in real time) determined the prevalence of pathological alleles CPOX, CYP1A1 and the frequency of sulfotransferase gene polymorphism.

Analysis of the information was carried out with the help of Statistica 6.0 and specialized software, coupled with MS Office applications. We compared high-quality binary attributes with the help of nonparametric statistics including building and analysis of two-dimensional contingency tables using chi-square ($\chi 2$). To compare the groups by quantitative characteristics, we use a two-sample t-test. Evaluation of relationships between the characteristics was performed with the help of one-way ANOVA (for qualitative characteristics) and regression analysis (for quantitative variables).

Results of the research. Analysis of the health situation on the basis of the monitoring studies has shown that the quality of drinking water in the area of residence of the children from the observation group exceeded the hygienic standards: for chloroform – up to 2.70 MAC;

residual free chlorine - up to 2.20 MAC; residual bound chlorine – up to 1.25 MAC; dichloromethane – up to 8.0 MAC, manganese - up to 3.3 MAC. In the area of residence of the control group, the quality of the drinking water was within the hygienic standards.

Assessment of the health risks associated with low-quality of drinking water in terms of hyperchlorination products and manganese, revealed the presence of inacceptable risk (HI=1,75-2,18) of nervous and hepatobiliary tract pathologies.

In the course of anamnestic study, we determined that the children under study were born from 1-3 pregnancy, did not have any in-born gastrointestinal system pathologies, were carried to full time (95% - observation group, and 94.4% - comparison group; p=0,34), had similar body-rate ratios (3241.3±154.6г and 51,2±0,6 cm – observation group; 3132.4±162.4 g и 50.37±1.56 cm – comparison group; p=0.43-0.48) and Apgar score (8.12±0.20 points versus 8.58±0.10 points; p=0,20). The frequency of acute intestinal infections in the two groups did not differ (10.3% and 12.5%, respectively, p = 0.67). In the observation group, monthly income per family member ranged from 4 001 to 7 000 rubles in 41.7% of the households (in the comparison group - 34.5%, p = 0.42), less than 4 000 rubles – 42% (52.4% in the comparison group, p = 0.08), more than 7 000 rubles - 16,3% (13,1% in the comparison group, p = 0.08). Most of the children (79.3% and 73.2%, respectively, p = 0.37) had comfortable housing conditions and used tap water without further purification (95% and 87.5%, respectively, p = 0.24). Eating disorders were registered in 32.8% of children from the observation group and 25% - from the comparison group (p = 0.29). The average length of the disease in the groups under study was 2,1 ± 1,1 g and 1,9 ± 1,2, respectively (p = 0.72).

A chemical blood test showed that the level of manganese in children of the observation group reached 0.0283 ± 0.0042 g / cm3 (reference concentration - 0.011 g/cm3, p < 0.01), and chloroform – 0.019891 ± 0.006,675 g/cm3 (reference concentration - 0.0 g/cm3, p < 0.01). In the comparison group, the level of manganese did not exceed 0.0110 ± 0.0004 g/cm3 (P = 0.78 to the reference), and chloroform - 0,001801 ± 0,000001 g / cm3 (P = 0.89 to the reference). In general, the level of manganese in the blood of the children in the observation group was 2.6 times higher than in the comparison group (p < 0.01), and chloroform - 10 times (p < 0.001).

Comparative analysis of the frequency of gastrointestinal complaints showed that the children from the observation group had more cases of decreased appetite (91.4% and 61%, respectively, p = 0.04), belching (45.5% vs. 25.4%, p = 0, 03), abdominal pain (58.6% vs. 37.2%, p = 0.03), localized in the epigastric (58.2% vs. 23.2%, r≤0,001) or right upper quadrant (61.2% vs. 32.1%, r≤0,001), stool disorders (78.5% vs. 57.1%; p = 0.004). Asthemo-vegetative complaints included: sweating (37.1% vs. 10.9%, p = 0.02), fatigue (16.4% and 8.6%, respectively, p = 0.04), and vehicle intolerance (6.9% and 5.4%, p = 0.82). In the observation

group, the symptoms of hepatobiliary dysfunction were detected 1.4 times more often as compared to the comparison group (87.9% and 64.3%, respectively, p = 0.001). We determined a significant causal relationship between the probability of biliary tract diseases and higher blood chloroform (R2 = 0,293-0,448; F = 15,348-36,392; p = 0.001), and functional disorders of the nervous system - and a high level of manganese and chloroform (R2 = 0.50-0.77; F = 93.67-109.62; p = 0.01-0.001).

Aethonium prevailed among other vegetative tones in the children from the observation group (50%), however vagotonic tone was determined in 37.5%, which is 1.9 times higher than in the comparison group (20%, p = 0.02). In the observation group, sympathicotonic type of autonomic reactivity was observed only in 25% of the children, which is 1.2 times less frequent than in the comparison group (30%, OR = 1.2, CI = 1.1-1.7), the predominant type is again hypersympathicotonic (62.5%); in the comparison group it is registered 1.5 times less often – in 43.3% (OR = 1.45; CI = 1,16-3,11). We established the following direct significant relationship: "elevated level of manganese in blood - the development of the original vagotonia and hypersympathicotonic-type autonomic reactivity (R2 = 0.37-0.42; F = 87.54-118.12; p = 0.01).

During an ultrasound scan of the hepatobiliary area, reactive changes of the liver in the observation group were recorded 7 times more often (31.7% vs. 4,5%, p = 0,01); in addition, there was a 1.6-1.7 times higher frequency of biliary dysfunction of the hypokinetic type (80.2% vs. 50%, p = 0.001) and an increase in the linear dimensions of the liver (12.2% and 7.0%, respectively, OR = 1.74; CI = 1.32-3.76). We registered a significant dependency between elevated blood levels in children and the development of chloroform reactive changes in the liver (R2 = 0.39; F = 76.83; p = 0.01), as well as between a higher manganese content in the blood and the presence of biliary dysfunction of the hypokinetic type (R^2 = 0.41; F = 99.23; p = 0.01).

During an ultrasound scan of the gastroduodenal area, a moderate amount of fluid in the stomach in children in the observation group was determined 3 times more frequently than the comparison group (33% and 11%, respectively, p = 0.003). A physiological variant of the gastric and duodenum motor functions in children from the observation group was registered half as often (14% vs. 28%, p = 0.03). Duodenogastric, duodenobulbar, and bulbogastric refluxes were diagnosed 1.4-1.5 times more frequently in the observation group (OR = 1.41-1.52; CI = 1.12-3,87). We established a causal relationship a high manganese level in blood and impaired gastric and duodenum motor functions (R^2 = 0.25-0.52; F = 46.5-119.18; p = 0.01-0.001).

During an electroencephalographic study, we found that modifications in the biorhythmic parameters of the brain cord in children from the observation group were recorded 2 times more often (55.5%) than in the control group (27.3%; OR = 2.03; CI = 1.64 -3.85) and had a mostly cerebral, functional character.

A study of biochemical indices in the children from the observation group showed signs of oxidative stress: the level of lipid hydroperoxide in serum was at 325.44 ± 23.72 mol / dm3 and MDA – 3.54 ± 0,117 micromoles/cm^3 that is 1,5-1 7 times higher than in the comparison group (p = 0.000-0.001); the frequency of documentation of the samples with elevated levels of lipid hydroperoxide was 28% in the absence of those in the comparison group, and MDA - 52%, which is 5 times higher than in the comparison group. We established a connection between a high level of lipid hydroperoxides and MDA - and the concentration of manganese in the blood (OR = 3.1-4.2; DI = 2.5-4.8; p = 0.001). The identified oxidative stress is caused by the depletion of the antioxidant defense resources to a subcellular level: glutathione peroxidase activity in the serum totaled 30.95 ± 3.31 ng/cm^3, Cu / Zn-superoxide dismutase 36.45 ± 2.16 ng/cm^3, which is 1.2-1.6 times lower than in the comparison group (p = 0.001-0.0001); additionally, the activity of glutathione peroxidase and glutathione-S-transferase was reduced by 1.2-1.4 times (p = 0.001). In general, the frequency of documentation of low levels of enzymes (51-55% of cases) was 3.8-4.2 times higher than in the comparison group (P = 0.001). The overall antioxidant status, as an integral figure in more than 50% of children from the observation group, reflected a pronounced decrease in the activity of antioxidant protection processes (125.64 ± 8.38 mol/dm^3, which is 2.2 times lower than in the comparison group, p = 0.000). We established a connection between the oppression of antioxidant processes and the levels of manganese and chloroform in the blood (OR = 2.6-5.1; DI = 2.0-6.1; p = 0.000). The contribution of manganese and chloroform to the imbalance in the antioxidant processes was 41-68%, (F = 16.19-425.05; p = 0.000-0.040). In the course of laboratory studies, we established an imbalance in neurotransmitters that regulate the processes of excitation and inhibition in the children from the observation group: a 1.5 times higher level of glutamate in the comparison group (148.87 ± 16.76 mmol/dm^3, p = 0.001) and a 2 times lower level of gamma-aminobutyric acid in serum (0.046 ± 0.013 mol/dm^3, p = 0.000); the frequency of documentation of the changes in the indices was 4.3-5.0 times higher than in the comparison group. We established a connection between an elevated level of glutamate couple with a lower level of gamma-aminobutyric acid and the level of manganese in blood (OR = 3.4-6.1; DI = 2.2-10.5; p = 0.000); the contribution of manganese to the imbalance in neurotransmitters is 64-79% (F = 145.06-287.55, p = 0.000). In addition, we determined that in the children from the observation group, the synthesis of hormones of the pituitary-adrenal axis was impaired (reduced levels of dopamine and cortisol – by 1.3 times, and serotonin - 2.0 times as compared to the comparison group), which has a significant connection with increased blood levels of manganese and chloroform (R^2 = 0.36-0.77; F = 28.74-94.62; p = 0.01). The results of the immunological study indicate a development of transient immunodeficiency in the children from the observation group (a 1.3-1.6 times decrease in phagocytosis, serum IgA, activity of the

T-lymphocyte component of the immune response, content of IgA in saliva, and a 1.3 times increase in serum IgEtotal as compared to the comparison group) significantly associated with high blood levels of manganese, and chloroform (R^2 = 0.33-0.63; F = 57.41-183.11; p = 0.01-0.001). Additionally, in the children from the observation group, we detected a 1.3-1.6 times higher frequency of the elevated levels of ALP, activity of the aspartic aminotransferase, pepsinogen 2 along with inhibited activity of pepsinogen 1, significantly associated with high blood levels of manganese, and chloroform (R^2 = 0.39-0.52; F = 33.67-121.76; p = 0.01-0.001). An immunogenetic study revealed the following: 10.3% of the children from the observation group had polymorphism of the sulfotransferase gene responsible for the detoxification of organic compounds; 13.8% had an abnormal allele CYP1A1 (cytochrome gene) responsible for phase 1 of the organic toxicants detoxification; 14.7% had a pathological allele CPOX (coproporphyrinogen oxidase) responsible for metalloprotein conjugation. It should be emphasized that the children with sulfotransferase gene polymorphism and/or pathological alleles CPOX and CYP1A1, had a 15-25% higher content of chloroform and manganese in blood as compared to the group average.

Discussion. The results of the conducted study show that in the areas with low-quality drinking water (in terms of exceeding the hygienic standards by the content of hyperchlorination products and manganese by 2.7 – 3.3 MAC), the risk of pathologies of the nervous system and hepatobiliary tract totals 1.75 – 2.18. The blood of the children consuming the water with higher levels of manganese and hyperchlorination products contains chloroform, and the level of manganese is 2.7 times higher as compared to the reference level (markers: blood levels of manganese and chloroform).

In children with inherited predisposition (10-15% of the population) (markers: pathological alleles SROH, CYP1A1, polymorphism of the sulfotransferase gene and the regulating processes of metals and organochlorine compounds detoxification), the level of manganese and chloroform in blood is 15-25% higher than in the children with no genetic defects.

Elevated levels of manganese and chloroform has a negative effect on the central and autonomic nervous systems, which is manifested in the imbalance in neurotransmitters and neurotransmitter homeostasis (markers: lower levels of serotonin, dopamine, cortisol, and gamma-aminobutyric acid, elevated levels of glutamate in blood due to higher concentrations of manganese and chloroform; R^2 = 0.36-0.79), a 2 times higher frequency of asthenoneurotic and autonomic disorders, mainly of parasympathetic type (markers: vagotonic type of initial vegetative tone with hypersympathicotonic variant of autonomic reactivity, impaired biorhythmic activity of the brain cord based on EEG, associated with an increased content of

manganese; R^2 = 0.36-0.42) (Fig.). Autonomic disturbances with a prevalence of parasympathetic effects in children are manifested in a biliary dysfunction syndrome and elevated levels of alkaline phosphatase in serum (markers: hypotonic type of biliary dysfunction based on ultrasound scan and an increase in alkaline phosphatase associated with the blood levels of manganese (R^2 = 0,52-0 61), which is aggravated during a direct influence of chloroform on the liver cells and the subsequent development of a reactive inflammatory process and functional disorders of the biliary tract of hypokinetic type (markers: reactive changes and enlarged liver on ultrasound scan, elevated AST associated with increased levels of blood chloroform; R^2 = 0.39-0.44). Autonomic dysfunction can cause disturbances in the gastric and duodenum motor functions with the development of reflux and regurgitation of duodenal contents into the stomach (markers: impaired gastric and duodenum motor functions, various types of reflux according based on an ultrasound scan associated with an increased level of manganese; R^2 = 0.25-0.52). The impact on the gastric mucosa of bile acids results in solubilization of the lipid membrane of the surface epithelial layers.

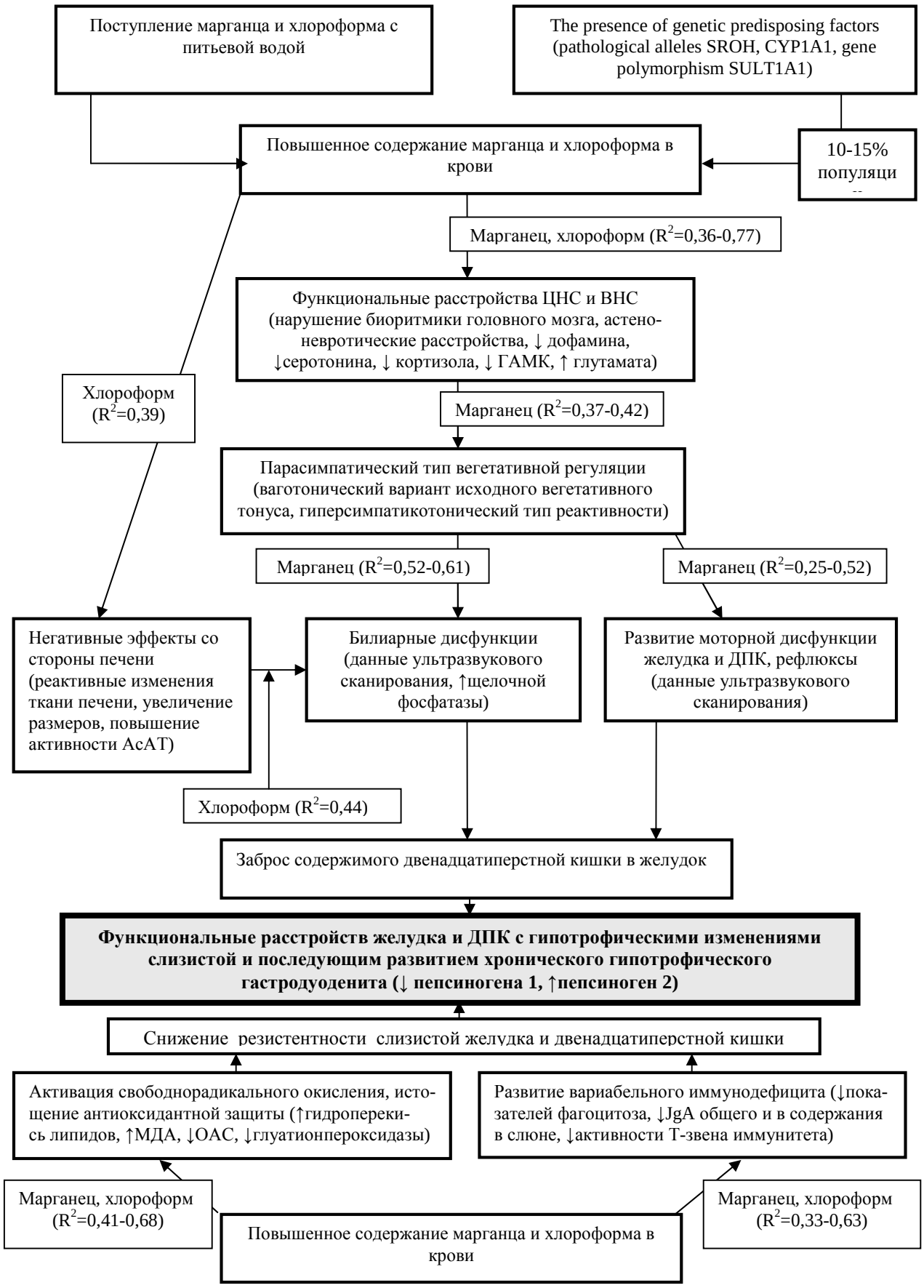

Figure. Pathogenetic features of the cascade mechanism of chronic gastroduodenal diseases caused by exposure to hyperchlorination products and manganese

According to the literature [2, 3, 6, 8], phospholipase pancreatic juice biotransforms lecithin contained in bile into lysolecithin which, when swallowed, has a pronounced cytotoxic effect on the epithelium and a subsequent development of hypotrophic processes (markers: reduction in pepsinogen 1, activation of pepsinogen 2). The inflammatory process in the gastric and duodenum mucosa is exacerbated by reduced resistance to the aggression factor (bile acids and lysolecithin), caused by the activation of free radical oxidation, decreased activity of antioxidant defense responses and impaired homeostasis of nonspecific resistance factors (markers: decrease of IgA in saliva, increase in serum lipid hydroperoxide, malondialdehyde, reduced overall antioxidant activity of blood serum, glutathione peroxidase, phagocytosis, JgA level, activity of the T-lymphocyte component of the immune response associated with higher blood levels of manganese and chloroform; R^2 = 0.33-0.68) (Fig. 1).

Thus, the pathogenetic basis of risk-associated gastroduodenal pathologies in the children consuming drinking water of inadequate quality containing hyperchlorination products and manganese is formed by morphological and functional changes in target organs (the central and autonomic nervous systems, liver) and the subsequent development of autonomic dysfunctions with motor impairments of the gastroduodenal and biliary areas along with oxidative stress and reduced non-specific resistance of the gastric mucosa. Pathomorphosis of the clinical manifestations of risk-associated gastroduodenal pathology includes the primary development of gastric and duodenal functional disorders along with the hypotrophic-type changes in the mucous and a subsequent development of chronic gastroduodenal pathology of the hypotrophic type. (ICD-10: K29.3-29.9).

The determined pathogenetic patterns of the development of risk-associated gastroduodenal pathology must be taken into consideration when development the programs for primary and secondary prevention in the children that consume low-quality drinking water in terms of hyperchlorination products and manganese.

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