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ISSUES IN STUDYING AUTONOMIC HOMEOSTASIS IN CHILDREN WITH ACUTE INTESTINAL INFECTIONS: A CASE STUDY OF SALMONELLOSIS

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Abstract: The involvement of reflex and humoral factors of the autonomic division of the central nervous system in the pathogenesis of intestinal infections, leading to the development of autonomic–visceral dysfunctions, has not been sufficiently studied. According to the theory of H. Selye and A.A. Koltypin, these dysfunctions have a phased nature and, regardless of etiology, are determined by the continuity in the functional activity of the main mechanisms of autonomic regulation of the body: sympatho-adrenal, parasympathetic, and humoral. We found no publications containing data on comprehensive research of these processes in children with intestinal infections, particularly in those with salmonellosis. The present work is a continuation of our previously published results of comprehensive studies.

Keywords: pathogenesis, phase characteristics, autonomic homeostasis, young children, severe forms of intestinal infections, cell membranes.

Research Objectives

The aim of this study was to investigate the clinical, biochemical, and instrumental indicators of autonomic homeostasis in 146 young children with salmonellosis. In this report, we present the results of the second part of the study, which includes clinical and instrumental findings, as well as the characteristics of structural and functional changes in cell membranes, using leukocytes as an example, given that the structural and functional organization of cell membranes is considered the final link in adaptive processes.

Materials and Methods

Clinical and anamnestic evaluation; general clinical laboratory methods (complete blood count, coagulation profile, electrolytes, glucose level); instrumental methods (cardiointervalography, electrocardiography, EEG); and the study of leukocyte cell membranes, including the analysis of interactions between cell membranes and specific membrane-tropic mediators of the autonomic nervous system and steroid hormones.

Results and Discussion

According to the theory of H. Selye and A.A. Koltypin, autonomic dysfunctions in acute pathological processes are characterized by a phased pattern, with an inevitable continuity in the

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functional activity of the leading mechanisms of autonomic regulation. Based on this concept, we considered it essential to study the clinical features of acute intestinal diseases, using severe forms of salmonellosis in young children as an example, in comparison with the state of the main regulatory mechanisms of adaptive processes—sympatho-adrenal, parasympathetic, and neurohumoral. Subsequently, identical studies were conducted in other acute gastrointestinal disturbances and intestinal infections, the results of which confirmed the conclusions of this study, indicating the universality of the findings. Detailed data will be presented in further publications.

The results obtained substantiated the working hypothesis.

A detailed analysis of the clinical and functional manifestations of salmonellosis in young children allowed us to identify distinct phases in the reactions of the autonomic nervous system to the toxin, which corresponded to the clinical manifestations of the disease. For this purpose, we used our original table of evaluative criteria for the clinical and pathophysiological manifestations of autonomic regulation in severe salmonellosis in young children, as previously published. Most children, both with gastrointestinal and generalized forms of the disease, were admitted with symptoms characteristic of the sympatho-adrenal phase. These included high body temperature, pale skin, dry mucous membranes, restlessness or agitation, frequent convulsions, tachycardia, elevated blood pressure, moderate dyspnea, and increased blood coagulation potential (hypercoagulation). Subsequently, the sympatho-adrenal phase was followed by the parasympathetic phase, which varied in severity and prognosis. With adequate therapy and clinical improvement, the parasympathetic phase was characterized by a restructuring of autonomic homeostasis that facilitated the restoration of normal physiological functions. However, in cases of unfavorable disease progression, the parasympathetic phase of salmonellosis was preterminal in nature, and unlike the favorable variant leading to recovery, it was associated with clinical manifestations of impending terminal conditions. The unfavorable course not only indicated a high risk of mortality but also predicted a significant likelihood of a prolonged disease course. Despite the overlap of several symptoms in both favorable and unfavorable parasympathetic phases, key differences with significant prognostic value were identified. A transition into the parasympathetic phase with a favorable prognosis was characterized by a reduction in general intoxication symptoms, a decrease in temperature to subfebrile levels, replacement of restlessness or agitation with lethargy, cessation of convulsions, moderately pronounced microcirculatory disturbances (mottled skin pattern, cyanosis of lips and nails, a positive Gvedal sign), proportional decrease in systolic and diastolic blood pressure, oliguria, frequent appearance of blood in stool, and a shift from hypercoagulation to hypocoagulation. In contrast, the transition into the parasympathetic phase with an unfavorable course was marked by a decrease in body temperature with a tendency toward hypothermia, predominantly reduced systolic and pulse pressure, bradyarrhythmia or, conversely, rhythm rigidity, dyspnea, anuria, hypocoagulation, pathological fibrinogen levels, presence of blood in the stool, “coffee-ground” vomiting, and occasionally intestinal bleeding—clinical signs consistent with grade II–III infectious–toxic shock, indicating a state of decompensation and exhaustion of adaptive mechanisms. These clinical observations were supported by cardiointervalography (CIG) data based on heart rate variability. According to CIG performed in the supine position at admission, most of the examined children exhibited a sympathicotonic initial autonomic tone (IAT).

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Table 1.

CIG Indicators in Children with Salmonellosis Depending on the Form and Phase of the Disease

Timing and Position During Examination		Analyzed Parameters				
		Mo, c	Амо %	Δx, c	ИН у.е.	$ИН_2/ИН_1$
Day 1	Supine position	0,40±0,05*** 0,30±0,05***	46,62±2,56*** 54,50±2,46***	0,10±0,02* 0,12±0,02*	591,1±38,16*** 708,7±41,27***	1,71±0,08*** 1,32±0,09
	Orthostasis (Standing position)	0,33±0,02*** 0,32±0,04*	60,08±3,11*** 50,61±2,73***	0,09±0,03* 0,09±0,01**	1013,7±59,21*** 935,2±52,61***	
Day 7	Orthostasis (Standing position)	0,75±0,05*** 0,98±0,14*	23,62±1,14* 35,76±1,71*	0,40±0,05* 0,29±0,07	40,8±5,81*** 63,1±7,04***	1,45±0,06 0,86±0,04***
	Orthostasis (Standing position)	0,37±0,04* 0,81±0,07**	21,34±1,56*** 23,04±1,04***	0,37±0,03* 0,26±0,06	77,9±6,24*** 54,3±6,22	
	Healthy children (S/P)	0,61±0,08 0,57±0,09	20,09±2,39 32,3±2,53	0,24±0,06 0,21±0,05	130,9±24,17 184,4±25,12	1,41±0,03

Note: The numerator shows data for patients with the gastrointestinal form, and the denominator represents those with the generalized form. Asterisks indicate statistically significant differences compared to healthy children: one asterisk – $p<0.05$; two asterisks – $p<0.01$; three asterisks – $p<0.001$.

Results

Initial sympathicotonia was observed more frequently in children with the gastrointestinal form of salmonellosis (71.43%) than in those with the generalized form (48.18%). In contrast,

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vagotonic initial autonomic tone (IAT) was more commonly detected in the generalized form (31.71%) compared to the gastrointestinal form (10.47%).

The predominance of initial sympathicotonia in patients with both forms of salmonellosis, but more pronounced in the gastrointestinal form, indicated activation of sympatho-adrenal compensatory mechanisms. Meanwhile, the relatively higher frequency of vagotonia in patients with the generalized form suggested depletion of the compensatory-adaptive mechanisms of the autonomic nervous system (ANS). The presence of eutonia in a small subset of patients did not imply absence of an ANS response to salmonellosis; clinical analysis in these cases revealed simultaneous activity of both sympathetic and parasympathetic divisions. These patients were primarily admitted during the transitional phase of the disease, clinically manifested by the onset of parasympathetic activation while sympathetic-adrenal signs were still partially present. This emphasizes the necessity of prioritizing clinical symptoms in evaluating autonomic status, with cardiointervalography (CIG) data serving as complementary information. CIG results obtained on Day 7 of hospitalization indicated a pronounced predominance of parasympathetic autonomic reactions in both patient groups, consistent with clinical findings. Among children with the gastrointestinal form of salmonellosis, 83.81% exhibited vagotonic IAT, whereas 85.37% of those with the generalized form demonstrated vagotonia; the remainder showed eutonia. Sympathicotonic IAT was virtually absent. Thus, by Day 7, most patients were in the parasympathetic phase of the disease.,CIG performed on Days 1 and 7 in the standing position, using the IN2/IN1 coefficient to assess autonomic reactivity, revealed that at admission, asympathicotonic autonomic reactivity predominated in both gastrointestinal (36.19%) and generalized (46.34%) forms. By Day 7, the prevalence of asympathicotonic reactivity increased to 74.29% and 85.37%, respectively, with no cases of hypersympathicotonic reactivity among children with the generalized form and only 2.86% among those with the gastrointestinal form. These findings demonstrate depletion of compensatory sympatho-adrenal mechanisms during the parasympathetic phase. The depth of this depletion can be assessed via the IN2/IN1 coefficient; values below 0.66 in the presence of vagotonia and sympathicotonic reactivity predict a prolonged course of salmonellosis and a high risk of mortality. Further analysis of the phase-specific clinical manifestations of salmonellosis revealed a clear association with chronobiological patterns. The critical period generally occurs within the first three days, followed by a transitional phase within the approximate one-week rhythm, and finally, stabilization processes emerge within the nine-day rhythm, mitigating infectious toxicosis. Overall, the sympatho-adrenal phase is observed during the first three days, the next three days constitute a transitional period, and the subsequent three-day rhythm marks entry into the parasympathetic phase, assuming an acute disease course. In patients with the gastrointestinal form, the sympatho-adrenal phase lasted on average 3.33±0.30 days, and in the generalized form, 2.09±0.04 days; the parasympathetic phase averaged 13.05±0.85 and 17.90±1.5 days, respectively. In summary, clinical observations confirm the phasic nature of the infectious process, with a predictable shift from the sympatho-adrenal to the parasympathetic phase, and recovery characterized by eutonia. This aligns with the concepts developed by A.A. Koltypin and H. Selye regarding the stereotyped phasic reactions of the autonomic nervous system to infectious agents and other stressors. While the sympatho-adrenal phase exhibits primarily quantitative variation, the parasympathetic phase reflects enhanced activity of autonomic mechanisms supporting anabolic and reparative processes. However, parasympathetic mechanisms may occasionally lead to adaptive failure, posing life-threatening risks in children.

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This nuanced understanding of the phasic stress structure of salmonellosis should be considered in intensive therapy. The lability of the phases of infectious-toxic stress depends on multiple factors, including constitutional and genetic characteristics, virulence of the infecting agent, and the child's adaptive capacity. The phasic structure of infectious stress represents the organism's adaptive responses, organized hierarchically across higher autonomic mechanisms, intermediate systems (hemodynamics and blood rheology), and effector structures at the membrane-cellular and intra- and extracellular metabolic levels. To date, hemodynamic changes in pediatric salmonellosis have been sufficiently studied, as have blood rheology alterations, which our traditional studies confirmed. Further analysis of the functional activity and reserve of adaptive responses during salmonellosis, based on structural-functional changes in cell membranes, reinforced their significance in pathogenesis and recovery. Given that membranous damage underlies all infectious diseases, determining its depth and extent is critical to disease severity and outcome. Thus, we conducted a series of studies assessing the state of cell membranes, recognizing that their structural-functional organization represents the final link in adaptive processes. At the same time, no comprehensive framework has yet connected the clinical manifestations of acute intestinal diseases, including salmonellosis in young children, with disruptions in autonomic function (sympatho-adrenal and parasympathetic) and structural-functional abnormalities of cell membranes.

Table 2

Content and Ratio of Major Phospholipid Fractions in Leukocytes of Young Children with the Gastrointestinal Form of Salmonellosis During Disease Progression (nmol per 10^9 cells)

Indicators	Observation Period		
	Acute Phase	Recovery Phase	Healthy Children
LPC	10,90 ± 1,10***	8,96 ± 1,21*	5,81 ± 0,58
PS	2,69 ± 0,52*	3,67 ± 0,41	4,79 ± 0,66
SM	5,59 ± 0,77	5,32 ± 0,42	6,13 ± 0,89
PC	7,26 ± 0,80*	8,75 ± 0,81	9,38 ± 0,66
PE	2,08± 0,11***	2,29 ± 0,14*	2,68 ± 0,10
LOP/ HOP	0,41	0,46	0,48
PC/SM	1,48	1,02	0,62

Note: Abbreviations: LPC – lysophosphatidylcholine, PS – phosphatidylserine, SM – sphingomyelin, PC – phosphatidylcholine, PE – phosphatidylethanolamine, LOP – easily

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oxidizable phospholipids (PS + PE), HOP – poorly oxidizable phospholipids [PC + SM]. Asterisks indicate statistically significant differences compared to healthy children: one asterisk – $p < 0.05$, two asterisks – $p < 0.01$, three asterisks – $p < 0.001$.

Disadaptive Changes in Leukocyte Membranes

Disadaptive changes manifested as follows:

1. Reduction in easily oxidizable, metabolically active phospholipid fractions in leukocytes, which are primarily involved in peroxidation processes and mobilized to replenish the organism's energy reserves. This naturally decreases the metabolic functionality of cell membranes, as most membrane-associated enzymes responsible for cellular life processes are phospholipid-dependent.
2. Pathological lysis of cell membrane phospholipids, caused by excessive activity of endogenous phospholipases. Evidence of this was the accumulation of degraded phospholipid forms—lysoforms—within the membrane structure, as indicated by increased lysophosphatidylcholine (LPC). LPC may have secondary membrane-detergent effects and reduce the functional-metabolic activity of the cell membrane by blocking transmembrane transport and energy exchange processes.

Adaptive responses in the structural-functional organization of cell membranes during the clinical manifestation phase of salmonellosis included metabolic inertia of poorly oxidizable phospholipids. Changes in phosphatidylcholine content were moderate, while sphingomyelin levels did not significantly change ($p<0.05$). These shifts influence the ratio of easily oxidizable to poorly oxidizable phospholipid fractions, favoring the predominance of the latter.

The pathogenetic significance of these structural membrane changes is supported by a clear correlation between quantitative membrane alterations and disease severity; these changes were more pronounced in the generalized form of salmonellosis. Analysis of the dynamics of these changes during disease progression also highlights the crucial role of cell membrane repair in sanogenesis and achieving a favorable outcome. Restoration of membrane structure correlated with the resolution of clinical symptoms.

Studies of erythrocyte membrane interactions with prednisolone in the presence of the XTC probe revealed that during the acute phase of both forms of salmonellosis (more pronounced in the generalized form), glucocorticoid consumption increased, decreasing by the recovery period. This finding is consistent with the role of glucocorticoid hormones as mediators of sympatho-adrenal influences within the autonomic nervous system (ANS). Based on these results, the use of glucocorticoids in the acute stage of salmonellosis may be justified.

Furthermore, a clear sequential sensitivity of cell membranes to adrenaline and acetylcholine was observed. During the clinical manifestation (sympatho-adrenal) phase, membrane receptors were most responsive to adrenaline. In the phase of clinical improvement (parasympathetic phase of infectious stress), membrane receptor sensitivity to acetylcholine—the mediator of parasympathetic ANS mechanisms—increased. These findings confirm the previously described phasic-autonomic structure of infectious stress in children with salmonellosis.

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The phasic course of salmonellosis in children was also supported by correlations between functional activity indicators of major ANS mechanisms and the activity of specific mediator interactions with cell membranes over time.

In summary, from a pathophysiological perspective, salmonella infection in children represents a form of membrane pathology accompanied by pronounced autonomic disturbances. This conclusion underscores the importance of further research into interventions correlating pathophysiological changes with clinical management in children with salmonellosis.

Mana matningizning ilmiy va mukammal inglizcha tarjimasi:

Conclusions

1. Salmonellosis in young children exhibits a phasic course, with a predictable succession of autonomic clinical-pathophysiological manifestations and a sequential transition from the sympatho-adrenal phase to the parasympathetic phase.
2. Clinically, the sympatho-adrenal phase is characterized by typical intoxication: high fever, nervous system disturbances (restlessness, agitation, seizures), microcirculatory disorders (pale skin, moderate cyanosis of lips and nails, cold hands and feet), impaired central blood flow (tachycardia, elevated or normal blood pressure), dyspnea, reduced urine output, and changes in blood coagulation potential (hypercoagulation). The parasympathetic phase is characterized by a decrease in body temperature, transition from restlessness to lethargy, pronounced microcirculatory disturbances (marbled skin, pale-gray hue, cyanosis of lips and nails, cold extremities), brady- or tachycardia, muffled heart sounds, lowered blood pressure, dyspnea, decreased urine output, and a shift from hypercoagulation to hypocoagulation.
3. In severe salmonellosis, the parasympathetic phase can follow either a favorable course (leading to recovery) or an unfavorable course. In the latter, characteristic clinical symptoms of this phase progress, reflecting exhaustion of adaptive mechanisms and manifesting as infectious-toxic shock.
4. The phasic nature and severity of autonomic clinical-pathophysiological manifestations correlate with cardiointervalography data, which can serve as objective criteria for assessing disease severity.
5. The peak period of clinical manifestations in children is accompanied by changes in the structural-functional organization of cell membranes, which include adaptive changes (accumulation of poorly oxidizable phospholipid fractions in the lipid bilayer) and disadaptive changes (accumulation of lysophospholipid forms).
6. Structural-functional reorganization of cell membranes in salmonellosis also involves altered sensitivity of membrane receptors to mediators of the sympatho-adrenal and parasympathetic divisions of the autonomic nervous system—adrenaline and acetylcholine—as well as to prednisolone as a mediator of sympatho-adrenal influences. These changes closely correspond to autonomic phases of the pathology: increased sensitivity to adrenaline and prednisolone is observed during the sympatho-adrenal phase, while increased sensitivity to acetylcholine is observed during the parasympathetic phase.

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