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Perioperative treatment of Hirschsprung's disease in children

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Summary

The aim of this work: to evaluate the eff ectiveness of the developed methods of perioperative treatment of Hirschsprung's disease in children.

Materials and methods. The study was conducted on the basis of the 2nd SamMI clinic in the period from 2002 to 2022. The obtained data were compared by correlation analysis with clinical and laboratory indices and with changes in solar activity by Wolf's numbers of the period of child embryogenesis, data of Murmansk Department of HMP).

Results. The results of the study of the activity of redox enzymes have established the following. When comparing the enzyme spectrum of the affected intestine and intact muscle, only a difference in the activity of SDH and LDH is revealed. Taking into account the activity of all enzymes in relation to the activity of SDH, it can be noted that alternative energy sources have a greater specific weight in the intestinal mucosa than in the muscle.

EDN: PDOZHH

Keywords: Hirschsprung's disease, Krebs cycle, solar activity, Wolf's numbers, agangliosis segment, hypoxia

Conflict of interests. The authors declare no conflict of interest.

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Дооперационное лечение болезни Гиршпрунга у детей

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Резюме

Цель данной работы: оценить эффективность разработанных методов дооперационного лечения болезни Гиршпрунга у детей.

Материалы и методы. Исследование проводилось на базе 2-й клиники SamMI в период с 2002 по 2022 год. Полученные данные были сопоставлены методом корреляционного анализа с клинико-лабораторными показателями и с изменениями солнечной активности по числам Вольфа периода эмбриогенеза ребенка, данные Мурманского отделения НМР).

Результаты. Результаты исследования активности окислительно-восстановительных ферментов установили следующее. При сравнении спектра ферментов пораженного кишечника и интактной мышцы выявляется только разница в активности SDH и LDH. Принимая во внимание активность всех ферментов по отношению к активности SDH, можно отметить, что альтернативные источники энергии имеют больший удельный вес в слизистой оболочке кишечника, чем в мышцах.

Ключевые слова: болезнь Гиршпрунга, цикл Кребса, солнечная активность, числа Вольфа, сегмент аганглиоза, гипоксия

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Introduction

Many issues of diagnosis and treatment of Hirschsprung's disease have been solved, but despite this, every 3rd operated patient has immediate and long-term complications, and every 20th child dies [1,4,10]. Up to 4–5% of radically operated patients require reconstructive surgery [7,9,12]. And if the local cause of Hirschsprung's disease in the form of an aganglionic non-functioning zone in the distal colon is sufficiently studied histomorphologically and histochemically [3,6,13], the researchers have almost not yet touched the general changes in the patient, metabolic disorders, which are an important link in the pathogenesis and without which we cannot build a rational and pathogenetically sound therapy [18,8].

Materials and methods

The activity of succinate dehydrogenase (SDH), lactate dehydrogenase (LDH), malate dehydrogenase (MDH), isocitrate dehydrogenase (iso-CDH), α-glycerophosphate dehydrogenase (α-GPDH) was determined in 37 patients with Hirschpung's disease by quantitative histochemical method[5,6,7], β-oxybutyrate dehydrogenase (β-OBDH), glutamate dehydrogenase (GDH), glucose-6-phosphate dehydrogenase (G-β-PDH), and inosium-5-phosphate dehydrogenase (I-5-PDH) in the intestinal mucosa removed during surgery and the transverse striated muscle taken during abdominal wall tissue dissection. The number of micromoles of formazan formed by 1 mg of protein in 1 min (Q- μmol formazan/ 1 mg protein in 1 min at 37 °C) was taken as the conventional unit of activity. In peripheral blood lymphocytes, SDH activity in blood smears taken before the operation was determined by a quantitative cytochemical method [5,7]. The obtained data were compared by correlation analysis with clinical and laboratory indices and with changes in solar activity by Wolf's numbers of the period of child embryogenesis, data of Murmansk Department of HMP) [7,14].

Results

The results of the study of the activity of redox enzymes have established the following. When comparing the enzyme spectrum of the affected intestine and intact muscle, only a difference in the activity of SDH and LDH is revealed. Taking into account the activity of all enzymes in relation to the activity of SDH, it can be noted that alternative energy sources (oxidation of fatty acids. amino acids, etc., except I-5-FDG) have a greater specific weight in the intestinal mucosa than in the muscle. Of course, histochemical features of the objects should be taken into account, but higher SDH activity in the proximal part of the intestine convinces one that the energy metabolism in the affected segment is really disturbed and signs of hypoxin (low SDH activity) appear [2,5,6].

Another feature of the histochemical spectrum of enzymes deserves attention: the activity of iso-CDG (the beginning of the Krebs cycle). This indicates in favor of a certain physiological role of the recently described Brownstein Krebs-Kondrashova cycle, which includes transaminase. SDH, fumase, MDH, etc., and functions without tricarboxylic acids [18,19]. The gut and the muscle form a functional (metabolic) system manifesting itself in ergonomic (working) correlations. The activity of muscle LDH has a certain diagnostic value because it correlates with the length of the affected agangliosis segment. The higher the LDH activity, the shorter the affected segment ($r = -0.576$, $p << 5\%$). This means that one can determine the severity of the process and, to some extent, the size of the lesion by the strength and endurance of the muscle. Practically, this is important when observing a child in dynamics. Increased activity of SDH and LDH in the proximal (dilated) part of the intestine, apparently, can be regarded as a compensatory process.

Under aerobic conditions, it is known that cytoplasmic NAD-H formed by oxidation of metabolites is re-oxidized with the help of shuttle systems (α-glycerophosphate and malate shunts) and the respiratory chain, which wins B competition with LDH for cytoplasmic NAD-H. Consequently, the increase in hypoxia. intoxication, the severity of the patient's condition in general may be characterized by a decrease in the activity of SDH and a compensatory increase in the role of anaerobic metabolism [2,5,11].

When analyzing the age-related dynamics of SDH activity, a significant change in the "ontogenetic curve" of all the objects studied attracts attention. The greatest distortion of the life cycle shortening is observed in the affected part of the intestine: the maximum of the enzyme activity occurs at 4.9 years instead of the expected 18–20 years, i.e., the calculated maximum for most physiological functions [7,16,17].

The next shift in the normal course of ontogenesis was the enzyme status of blood lymphocytes of cells performing trophic function in the intestine (t max 7.5 years). The age maximum of muscle ADH activity shifted less noticeably, but nevertheless it can no longer be interpreted as intact (t max =12 years). The age dynamics of the proximal intestinal ADH is a certain difficulty due to the wide variation of the indices. However, it can be noted that in the compensatory part of the intestine there is a tendency to lengthen the ontogenetic cycle [15].

Of particular interest is the retro reconstruction of the enzymatic status during neonatal and intrauterine development. Extrapolation to the past shows that in the period of neonatality, the activity of SDH of the affected organ should be not less than the activity of muscle enzymes. This may indicate compensation of function in the affected organ during this period.

A certain heterochronism is observed in the maturation of various organ functions [20,22], but in general for the vital organs this difference in reaching the maximum of functions is relatively small. Thus, in Hirschsprung's disease, there is a pathological heterochronism of energy metabolism (and consequently physiological functions) of different systems. It can be assumed that individual cellular elements of the tissue show the same shortening of the life cycle. First of all, this is true for nerve ganglia of the large intestine. Here we see a thread that may lead to an understanding of the inconsistency often found in the clinic between the severity of manifestations of Hirschsprung's disease and the extent of intestinal lesions, namely, among other things, there is a dependence of the severity of clinical symptomatology and its manifestation in different age groups on the degree of ontogenetic cycle shortening of the enzymes studied.

Since the formation of Hirschsprung's disease begins intrauterine, we can assume that the early stages of ontogenesis are reflected in the enzyme status of the affected and healthy organ [2,21]. In this regard, of interest are the correlations we found between the activity of the studied enzymes and Wolf numbers during embryogenesis. In particular, we found a positive relationship of Wolf number at week 7 of gestation with the activity of SDH of the mucosa of the distal distal segment of the large intestine ($r=0.626$). At week 8, this correlation becomes even stronger ($r=0.672$). The most significant correlation was found at week 17 ($r=0.692$) of pregnancy. Further, positive but less strong correlations of SDH activity with the level of solar activity were found at all gestational periods.

The very sign of the relationship indicates that the primary lesion has received some but not complete compensation. Since solar activity causes hypoxia, from the 7th non-divided intrauterine development (formation of nerve ganglia in the intestinal wall, circular longitudinal muscles) to the 17th week (formation of crypts, villi with many bocalytic cells) all factors causing tissue hypoxia. Viral infections, severe emotional stress, chemicals, physical environmental factors, etc. – can provoke the occurrence of Hirschsprung's disease [1,2,7].

Hirschsprung's disease can only be cured by surgery. The issue of the necessity of surgical treatment has been resolved and is not controversial. However, it would be wrong to "short-circuit" the entire problem of treatment, because, on the one hand, the pathology is not limited to local changes in the colon, it is represented much wider; on the other hand, after resection of the aganglionic zone, additional treatment measures are required to fully restore intestinal function [18]. In-depth insights into the pathogenesis of Hirschsprung's disease, obtained as a result of our studies, gave reason to introduce metabolic drugs (metabolic aid) into the treatment of patients in order to regulate metabolic processes of cells and, in particular, to improve energy metabolism, eliminate tissue hypoxia. Since the latter plays a very important role in the pathogenesis of Hirschsprung's disease, this kind of therapy is very important in preparing patients

Table 1.
Metabolic therapy regimen

The drug	Method of introduction	Age, years	Daily dosage	Analogue for oral administration	Daily dosage
Cocarboxylase	I/m, I/v	1–3 4–7 8–14	0.012×1–2 times 0.025×1–2 times 0.05×1–2 times	Benfotiamine	0.005×2–3 times 0.005×4 times 0.025×2 times
Riboflavin-mononucleotide	I/m	1–3 4–7 8–13	1% solution 0.25ml×1–2 times 1% solution 0.5ml×1–2 times 1% solution 1ml×1–2 times	The same solution is given sublingually or behind the lip in doses corresponding to parenteral	
Nicotinamide	I/m, I/v	1–3 4–7 8–14	1% solution 1ml×1–2 times 1% solution 1ml×1–2 times 2.5% solution 1ml×1–2 times	Nicotinamide	0.01×2–3 times 0.025×4 times 0.05×2 times
Lipoic acid	I/m, I/v	1–3 4–7 8–14	0.5% solution 1ml×1–2 times 0.5% solution 2ml×1–2 times 0.5% solution 3–4ml×1–2 times	Lipoic acid Lipamide	0.012×2–3 times 0.012×4 times 0.025×2 times
Calcium pantothenate	I/m	1–3 4–7 8–14	20% solution 0.5ml×1–2 times 20% solution 1ml×1–2 times 20% solution 1ml×1–2 times	Calcium pantothenate	0.1×2–3 times 0.1×3–4 times 0.02×3 times
Panangin (Asparkam)	I/V drip with 5% glucose	1–3 4–7 8–14	2–4 ml 5–6 ml 7–10 ml	Panangin (Asparkam)	¼ tablet×2–3 times ½ tablet×2–3 times 1 tablet×2–3 times

for radical elective surgery. As well as in the period of rehabilitation. It contributes to improvement of metabolic processes in cells and tissues, improvement of intracellular and cellular regeneration and thereby prevention of postoperative complications, greater resistance of patients to respiratory and other infections, the ability to sharply reduce the use of antibiotics, improve recovery processes.

The complex of cofactors and substrates that improve cell and tissue energy include the following drugs: thiamine pyrophosphate in the form of cocarboxylase, riboflavinmononucleotide or flavinite, nicotinamide, calcium pantothenate, lipoic acid or lipamide, panangin. The drugs regulate the 2 most important steps of the Krebs cycle, they are synergistic, so they are administered as a single complex. The parenteral route of administration of at least part of the drugs in therapeutic dosages corresponding to age is more effective (see Table 1).

The course of the complex of drugs is designed for 7–10 days before surgery, 7–10 days in the postoperative period and 7–10 days every 1.5–2 months for the next year after surgery. The recommended doses and duration of courses are developed under the control of cytochemical parameters.

In some cases the complex of drugs can be expanded by cofactors and substrates involved in metabolic regulation of lipids, synthesis of purines and pyrimidines, which contributes to stabilization of cell membranes and their organelles, heme formation in hemoglobin, activation of phagocytic function of neutrophils, better regeneration of cellular structures.

In addition to the one presented above, the 2nd complex was developed, which includes the following preparations: pyridoxalphosphate (intramuscular), cyanocobalamin (intramuscular), folic acid (orally), calcium pangamate (orally), methylmethionine sulfonium chloride, or vitamin U (orally), glutamic acid (orally), potassium orotate (orally), histidine (intramuscular), riboxin (orally) in age dosages of 5–7 days. At the same time, potassium orotate and riboxin should be administered in the first hours and the first 2 to 3 days after surgery. Panangin, glutamic acid or preparations of the 1st (main) complex can provide energetic assimilation of these nitrogenous bases.

Utilization of preparations of the 2nd complex requires providing cells and tissues with energy. Therefore, it is advisable to administer them after 7–10 days of treatment with metabolites and cofactors of the 1st complex, aimed at improving tissue energy.

Conclusions

Thus, intensive preoperative preparation using the whole complex of measures is required for patients admitted in decompensated or subcompensated stages of the disease. In all the cases we observed in a relatively short period (25–30 days) we managed to achieve a positive therapeutic effect, improvement of the general condition of children with normalization of homeostasis, a noticeable increase in body weight. This largely predetermined the success of the radical surgical intervention. There were no postoperative complications and no lethal outcomes. Long-term functional results at 2 years and more after surgery were good and satisfactory.

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