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## PECULIARITIES OF SYNTROPIC FUNCTIONAL DISORDERS OF THE DIGESTIVE SYSTEM AGAINST THE GROUND OF CONNECTIVE TISSUE DYSPLASIA

**Abstract.** A considerable occurrence of functional gastrointestinal disorders (FGID) in childhood, their frequent combination between themselves, the risk of transformation into organic pathology together with high collagen content in the digestive organs require investigation of pathophysiological relations of the pathology with collagen dysfunction. Objective of the study is to investigate the role of collagen disorders in FGID pathophysiology and assess their effect on clinical development of irritable bowel syndrome. 63 children suffering from FGID have been examined. Irritable bowel syndrome was diagnosed as a leading functional disorder of all the children examined. Syntropic functional biliary disorders were found in (38,46±6,13) % patients. By the results of molecular-genetic examination genetic polymorphism of COL3A1 rs1800255 with prevailing the genotype G/A – 47,62 % (95 % CI 35,04 – 60,2) was determined, that was most reliably found ( $p = 0,008$ ) in children with syntropic functional biliary disorders and was associated with a wide range of comorbid pathology ( $p = 0,002$ ) and pronounced dysplastic signs ( $p = 0,034$ ).

**Key words:** children, functional gastrointestinal disorders, irritable bowel syndrome, connective tissue dysplasia, collagen of III type (COL3A1), syntropic pathology.

**Introduction.** Nowadays functional gastrointestinal disorders (FGID) are considered as the most spread pathology of the gastrointestinal tract (GIT) in childhood, with morphological and physiological disorders in its base associated with visceral hypersensitivity, motor disorders of the gastrointestinal tract, protective mucous barrier, immune function and intestinal microbiota content, as well as disorders of the central nervous system. The last version of the document "Roman Criteria IV" (2016) defines FGID as disorders of gut-brain interaction [2].

"Roman Criteria IV" officially recognized overlap syndrome, that is possible availability of several functional disorders at the same time and transition of one form into another one, for example, combination of irritable bowel syndrome with functional dyspepsia [2].

Today irritable bowel syndrome (IBS) is considered to be the most spread and examined pathology among FGID as a standard for understanding pathogenic essence of FGID.

Synthesis disorders of the cerebral and intestinal peptides, genetic susceptibility to pro-inflammatory response, increased permeability of the intestinal epithelial barrier, excessive receptor sensitivity of the mucous membrane, changes from the side of immune reactivity and intestinal microbiota make pathophysiological morphological and biochemical basis promoting development of IBS signs [1, 3, 6].

The role of collagen dysfunction in pathogenesis of syntropic diseases of the digestive system and FGID in particular is not studied adequately. Considering high collagen content in the organs of the gastrointestinal tract, the effect of connective tissue dysplasia on the development of digestive pathology has become of an important value. Connective tissue dysplasia is known to cause structural abnormalities of the internal organs, motor disorders and changes of functional possibilities, which together with circulatory peculiarities result in inadequate reparative mechanisms and synchronization of

inflammatory processes in the body [4].

**Objective:** to investigate the role of collagen disorders in FGID pathophysiology and assess their effect on clinical development of irritable bowel syndrome.

**Materials and methods.** 63 children at the age from 2,5 to 16 years were examined (an average age –  $8,9 \pm 4,5$  years), including 36 girls and 27 boys. Inclusion criteria were age of children from 1 to 18 years and diagnosed FGID. Exclusion criteria were the age under 1 year, anxiety signs available (“red flags”), congenital or acquired immunodeficiency conditions.

In addition to general clinical examinations certain phenotype signs were determined in all the children, the degree of connective tissue dysplasia was assessed in the total sum of score by means of the diagnostic criteria suggested by L.M. Abbakumova et al. (2006). According to these criteria the mild degree of connective tissue dysplasia is no more than 12, moderate degree – no more than 23, severe degree – 24 and more.

At the same time molecular-genetic examination was performed with determination of gene polymorphism of collagen III alpha 1 type (COL3A1) rs1800255 in the cells of the buccal epithelium of the patients examined. The concentration and purity of DNA specimen were determined on the spectrophotometer (Nanophotometr, Implen). Polymorphism of COL3A1 rs1800255 2092G>A was assessed by means of polymerase chain reaction method – polymorphism of restriction fragments length (PCR-PRFL). Genotyping of COL3A1 polymorphism in the nucleotide position – 2092 was performed

with the use of primers: direct F GCC CCA GGA CTT AGA GGT G and reverse R CCT TGC AGA CCA GGA GT (Ltd «Synthol», Russia).

The results obtained were statistically processed by means of Windows XP applying the licensed software Microsoft Excel XP. The following indices were calculated: arithmetic mean value, arithmetic mean standard error, representative relative value error, Pearson  $\chi^2$  criterion, Yates correction, odds ratio (OR), 95 confidential interval (CI). Reliability of results was considered to be determined in case its probability was no less than 95 % ( $p < 0,05$ ).

**Results.** Certain age peculiarities were determined by the results of the study. The 1<sup>st</sup> junior age group appeared to be have the least number of children ( $12,7 \pm 4,2$ ) % out of all the examined ones. All the following age periods were characterized by an increased number of patients with maximum in the senior group ( $36,5 \pm 6,1$ ) %, which is practically three times as much as the juniors. It must be explained by a number of negative factors at older age, including feeding disorders, excessive psychophysical exertion, reduced parental control, appearance of bad habits etc. There were more girls among the examined patients ( $57,14 \pm 6,23$ ) % than boys ( $42,86 \pm 6,23$ ) %,  $p > 0,05$ , which is demonstrated on the diagram below.

Diagnosis of FGID in the examined patients was made according to Roman Criteria IV, which define irritable bowel syndrome (IBS) as a leading functional disorders of all the patients. Clinical variant of IBS with prevailing constipation was diagnosed in the majority of patients (76,92 %),

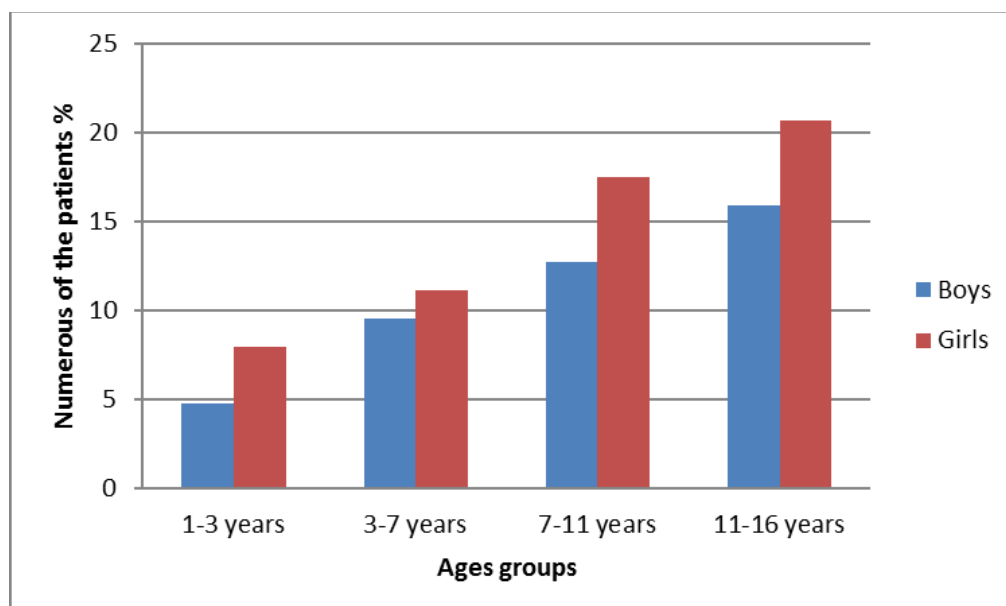


Fig. 1. Distribution of the examined children by gender content and age

the variant of IBS with prevailing diarrhea was diagnosed in the rest of children (23,08 %).

Syntropic pathology of the digestive organs was found in (84,13±4,6) % of the examined patients. Syntropic functional biliary disorders (FBD) were found practically in one third of patients with IBS (n=24) (38,1±6,12) %, which enabled to isolate those patients into a separate clinical group (IBS + FBD) for further comparative analysis.

Syntropic conditions of the digestive organs in children with IBS include functional dyspepsia – (17,95±6,15) %, disorders of the exocrine function of the pancreas (secondary exocrine insufficiency) – (28,21±7,21) %, developmental defects of the gallbladder (flexure, strangulation) – (41,03±7,88) %. In addition to syntropic pathology of the digestive system a number of comorbid diseases of other organs were found: allergic diseases (bronchial asthma, allergic rhinitis, atopic dermatitis) in (28,21±7,21) %, allergic reactions (urticaria, Quincke’s edema) to food and pharmacological means (41,27±7,88) %, minor defects of the heart development (MDHD) (abnormal chorda of the left ventricle, prolapse of the mitral valve) in (15,38±5,78) %, chronic tonsillitis – in (17,95±6,15) %, neurocirculatory dystonia (ND) – in (5,13±3,53) % of patients. Dysmenorrhea and developmental defect of the reproductive system (duplex uterus) were found in one patient.

The following pathology was found in children from IBS + FBD group: developmental defects of the gallbladder (DDG) in the majority of the examined patients – (87,5±6,75) %, disorders of the exocrine function of the pancreas (DEFP) – in (66,67±9,62) %, secondary acetone syndrome (AS) – in (45,83±10,17) %, neurocirculatory dystonia – in (25,0±8,84) %, allergic diseases (allergic rhinitis) – in (25,0±8,84) %, minor defects of the heart development (atypical chorda of the left ventricle)– in (20,83±8,29) %, chronic subcompensated tonsillitis – in (12,5±6,75) %, instability of the cervical region of the vertebral column was diagnosed in one case.

The conducted analysis (Fig. 2) detected statistically reliable ( $\chi^2 = 13,24$ ;  $p = 0,000$ ) relations between the rate of abnormalities of the gallbladder as one of the visceral signs of CTD and availability of FBD in the examined patients, which reflects frequent development of bile ducts disorders against the ground of dysplastic changes of the biliary tract. Secondary insufficiency of the pancreas prevailed in children from IBS + FBD group ( $\chi^2 = 8,97$ ;  $p = 0,003$ ), which gives the evidence of close functional interrelations of the biliary tract and pancreas. Statistically reliable relations ( $\chi^2 = 8,5$ ;  $p = 0,001$ ) were found between FBD and development of metabolic disorders in the form of secondary acetone syndrome that in this group of patients was provoked by dietary

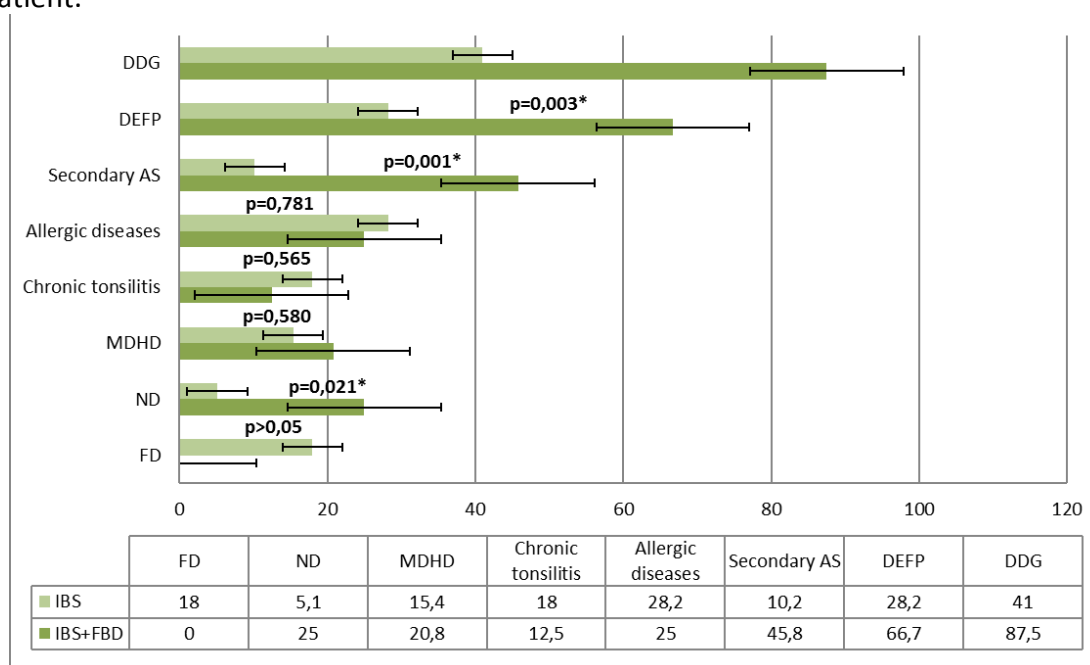


Fig. 2. Comparative characteristics of comorbid pathology in clinical groups

Notes: GDD – gallbladder developmental defects; DEFP – disorders of the exocrine function of the pancreas; AS – acetone syndrome; MDHD – minor defects of the heart development; NCD – neurocirculatory dystonia; FD – functional dyspepsia. \* differences are reliable

disorders mainly (excessive intake of fatty food, overeating). According to our findings the signs of neurocirculatory dystonia were registered more often in children with FBD ( $\chi^2 = 3,65$ ;  $p = 0,021$ ). Functional dyspepsia was diagnosed in 7 patients possessing similar pathogenic mechanisms with IBS which are mainly manifested by disorders of the motor functions of the gastrointestinal tract and visceral hypersensitivity. Overlap of several functional diseases available is a peculiar characteristic of patients with CTD.

Probably a wide spectrum of comorbid pathology reflects a degree of dysplastic shifts. While assessing phenotype signs of CTD clinically valuable signs (2, 3 degree of severity) were found in (84,13±4,6) % of the examined patients. As the analysis demonstrated, severity of CTD differed depending on the age of patients. Mild and moderate manifestations of CTD prevailed in children of a preschool age (n=16) (OR = 4,27 (95 % CI 1,32 – 13,82;  $p = 0,025$ )). At the senior age group (n=42) the number of children with pronounced signs of dysplasia (n=24) was reliably higher (OR = 0,23 (95 % CI 0,07 – 0,76;  $p = 0,025$ )).

Objective examination found certain differences by the occurrence of certain phenotype signs among the examined children in clinical groups (Fig. 3).

The data presented in the diagram are indicative of higher chances of the following CTD phenotype signs available in children with IBS + FBD: skin changes in the form of hyperextensibility and scars (OR = 0,17 (95 % CI 0,05 – 0,6;  $\chi^2 = 8,55$ ;  $p = 0,003$ )), weakness of the abdominal muscles (OR = 0,16 (95 % CI 0,04 – 0,6;

$\chi^2 = 8,48$ ;  $p = 0,004$ )), changes of the osseous-articulatory system – scoliosis (OR = 0,33 (95 % CI 0,11 – 0,96;  $\chi^2 = 4,25$ ;  $p = 0,039$ )), flatfoot (OR = 0,32 (95 % CI 0,11 – 0,92;  $\chi^2 = 4,66$ ;  $p = 0,031$ )).

In order to determine pathophysiological relations of collagen dysfunction with FGID molecular-genetic examination of patients was conducted with detection of carriage of COL3A1 rs1800255 2092G>A polymorphism. The results of the study found 26 patients (41,27±6,2) % to have G/G genotype variant, heterozygous (G/A) – in 30 (47,62±6,29) %, mutant variant (A/A – polymorphism in homozygous condition) – in 7 children (11,11±3,96) %. Analysis of the data obtained enabled to determine statistically valuable differences between clinical groups of patients: variant of G/G genotype prevailed in patients with IBS (n = 22) (OR = 6,47 (95 % CI 1,86 – 22,5;  $p = 0,004$ )), in comparison with the patients from IBS + FBD group (n = 4), while heterozygous variant (G/A) prevailed in patients with IBS + FBD– 66,67 % (n = 17), (OR = 0,21 (95 % CI 0,07 – 0,62;  $p = 0,008$ )). A/A variant of the genotype was found more often in patients from IBS + FBD (n = 4) (OR = 0,42 (95 % CI 0,08 – 2,05;  $p = 0,491$ )).

Analysis of the data obtained enabled to determine statistically reliable relations of the detected polymorphism (genotype G/A) with a number of comorbid diseases in the examined children, and visceral CTD signs in particular ( $\chi^2 = 9,48$ ;  $p = 0,002$ ): defects of gallbladder development in 22 patients (75,86±7,95) %, minor abnormalities of the heart in 6 ones (20,69±7,52) %, secondary insufficiency of the pancreas in 12

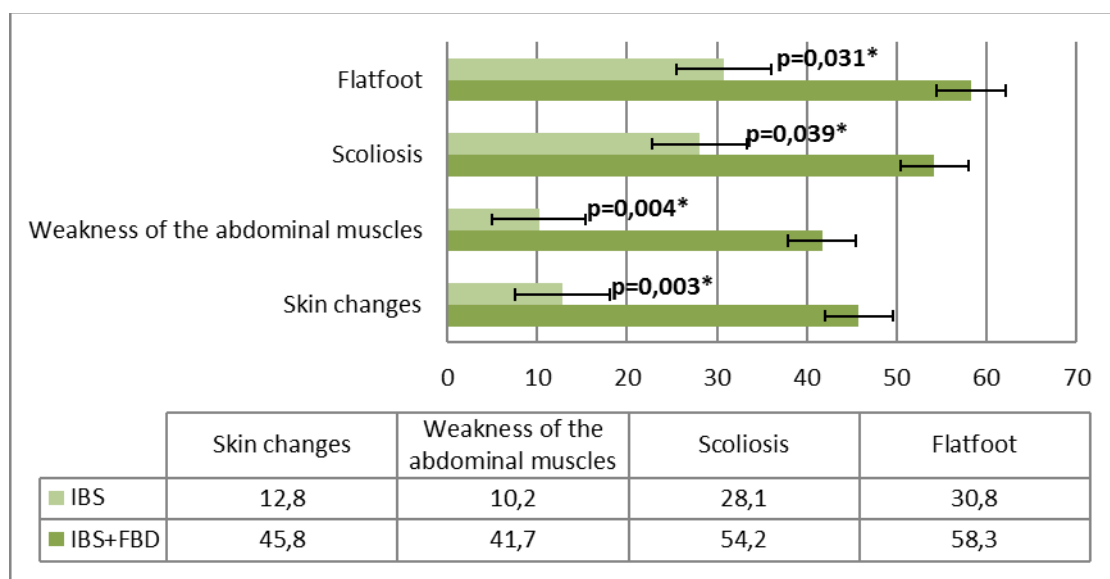


Fig 3. Rate of CTD phenotype signs in the examined children  
\* reliable differences

children (41,38±9,15) %, secondary acetonemic syndrome – in 10 (34,48±8,83) %, allergic pathology – in 9 (31,03±8,59) %, neurocirculatory dystonia – in 5 (17,24±7,01) %, functional dyspepsia – in 3 (10,34±5,65) %. Moreover, statistically valuable relations of G/A genotype with the degree of severity and pronunciation of phenotype signs of CTD ( $\chi^2 = 4,5$ ;  $p = 0,034$ ) should be mentioned here in children from IBS + FBD group.

**Discussion.** The study conducted have demonstrated a wide occurrence of syntropic pathology of the digestive organs in patients with CTD, first of all combination of irritable bowel syndrome with functional biliary disorders, which coincides with the data of other authors [5]. Dysplastic-dependent changes of the digestive organs with the development of motor disorders from the side of the intestines and biliary tract make up the ground for the development of secondary pancreatic insufficiency in patients with CTD, which is evidenced by the findings obtained. Predominance of patients from the older age group with pronounced signs of dysplasia reflects the progression of CTD development, which is characterized by inconsiderable amount and expressiveness of phenotype signs at birth. Although in the course of time at the period of the body development and growth under the influence of exogenous factors and lack of preventive measures new signs may occur and previous signs intensify. Defining of external phenotype signs of CTD should direct a diagnostic search to find visceral dysplastic changes, first of all from the side of the digestive organs due to high collagen content in them. Detection of COL3A1 rs1800255 polymorphism in the examined patients is indicative of its important role in pathophysiology of syntropic functional gastrointestinal disorders in children.

**Conclusions.** 1. Syntropic pathology in case of irritable bowel syndrome in the majority of patients 38,5 % (95 % CI 32,4 – 44,6) is manifested by functional biliary disorders, and with their availability reliable relations are determined with defects of gallbladder development ( $p = 0,003$ ), disorders of the pancreatic exocrine function ( $p = 0,003$ ) and metabolic disorders ( $p = 0,001$ ).

2. The most important phenotype signs of connective tissue dysplasia in children with irritable bowel syndrome are the following visceral disorders: developmental defects of the

gallbladder 75,86 % (95 % CI 67,91 – 83,81), minor developmental defects of the heart 20,69 % (95 % CI 13,17 – 28,21), as well as external signs of the: skin ( $p = 0,003$ ), muscles ( $p = 0,004$ ), osseous-articular – scoliosis ( $p = 0,039$ ), flatfoot ( $p = 0,031$ ), which were associated with functional biliary disorders available.

3. Genetic COL3A1 rs1800255 polymorphism was found in children with irritable bowel syndrome with prevailing genotype G/A – 47,62 % (95 % CI 35,04 – 60,2), which reliably more often ( $p = 0,008$ ) was found in children with syntropic functional biliary disorders and was associated with a wide spectrum of comorbid diseases ( $p = 0,002$ ) and degree of dysplastic changes ( $p = 0,034$ ).

**Prospects of further studies.** The results of a comprehensive examination with determined clinical, molecular-genetic peculiarities of syntropia with functional gastrointestinal disorders in children enable to elaborate differentiated management of such patients, and they require further investigations of other variants of collagen gene polymorphism in order to detect their role in the development of the mentioned pathology.

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