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CLINICAL MANIFESTATIONS OF GASTROINTESTINAL TRACT CHANGES IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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A - concept and design of the study, B - data collection, C - analysis and interpretation of data, D - writing an article, E - editing an article, F - final approval of the article

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Summary. *Juvenile idiopathic arthritis remains one of the most common chronic inflammatory rheumatic diseases of childhood. A significant proportion of patients experience nausea, vomiting, abdominal pain and loss of appetite with methotrexate therapy, which can significantly complicate the course of the disease.*

The aim *was to study the clinical and anamnestic signs of liver disorders in children, depending on the manifestations of juvenile idiopathic arthritis.*

Materials and methods of research. *The presence of gastrointestinal complaints, namely abdominal pain, loss of appetite, nausea and vomiting in 104 children with juvenile idiopathic arthritis who were treated at the State Institution "Institute of Child and Adolescent Health of the National Academy of Medical Sciences of Ukraine" was analyzed.*

Results. *According to the results of the study, children with juvenile idiopathic arthritis had gastrointestinal complaints in 47.12%. We find out that the majority of children had gastrointestinal complains at the age of 10–13 years (55.36%, $p < 0.001$), and at the onset of the disease after 15 years (100%, $p < 0.01$). Young children often complained of abdominal pain and vomiting, older children complained of loss of appetite and persistent nausea, regardless of the variant, activity, duration of arthritis and the presence of methotrexate in complex therapy. It was also found that appearance of gastrointestinal complaints were observed more often at a dose of methotrexate less than 10 mg / m^2 / body surface ($p < 0.05$).*

Conclusions. *1. We find out that in 47.12% children with juvenile idiopathic arthritis had gastrointestinal complaints, aged 10–13 years (55.36%; $p < 0.001$). The most amounts of complaints were common for patients older than 15 years old ($p < 0.01$). 2. The nature of the complaints varied and depended mainly on the age of the patients. Younger children had abdominal pain and vomiting simultaneously older children had decreased appetite and nausea. The presence of complaints did not depend on the variant, activity and duration of the juvenile idiopathic arthritis. 3. According to our study complaints were not due to the presence of methotrexate in combination therapy. Children complained much more often if methotrexate dose was less than 10 mg / m^2 than in the case of higher doses ($p < 0.05$).*

Key words: juvenile idiopathic arthritis, methotrexate

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Introduction

Juvenile idiopathic arthritis (JIA) is one of the most common chronic inflammatory rheumatic diseases of childhood [1-3]. Information on its prevalence in the world may vary slightly, depending on the region of residence [4-6]. The results of recent studies indicate that in Ukraine the incidence of JIA in children aged 0 to 17 years is

approximately 0.32-0.42 cases per 1,000 children [7].

The history of MTX dates back to 1948 with a report by Sidney Farber, but only forty years later in 1988 MTX was approved for the treatment of rheumatoid arthritis [8]. To date, the key drug for the treatment of JIA is methotrexate (MTX) - disease modifying antirheumatic drug (DMARD).

MTX dosage for JIA treatment are well defined worldwide and are 10–20 mg / m2 / body surface, once weekly orally or by injection, also in the modern scientific literature a dosage can be ranged 7.5–25 mg [9].

Based on the current literature, MTX side effects are described as: stomatitis, hair loss, fatigue, headache, gastrointestinal upset, nausea, diarrhea, and bone marrow suppression. It is also known that a significant proportion of patients experience nausea, vomiting, abdominal pain and loss of appetite caused by MTX therapy, which in particular provokes patients to stop taking the drug and is not always associated with MTX [10-12].

Thus, appearance of gastrointestinal complaints (GIC) and liver disorders still not enough analyzed in children with JIA.

The aim is to study clinical and anamnestic signs of liver disorders in children, taking into account the peculiarities of juvenile idiopathic arthritis.

Material and methods of research

We observed 104 children with JIA aged 10 to 18 years (13.3 ± 0.3) who were treated at the State Institution "Institute of Child and Adolescent Health of the National Academy of Medical Sciences of Ukraine." Gastrointestinal complaints, namely abdominal pain, loss of appetite, nausea and vomiting were analyzed in children with JIA.

All children with JIA were divided into groups according to gender, patients' age, age of JIA onset, variant of arthritis, duration of the JIA, disease activity and the Juvenile Arthritis Disease Activity Score (JADAS), namely JADAS-27, presence of methotrexate in treatment and its regimen.

Exclusion criteria were: children who had a systemic variant of the disease, juvenile ankylosing spondylitis or enthesitis-associated arthritis, concomitant endocrine diseases (diabetes, autoimmune thyroiditis, obesity) and gastrointestinal diseases. All examined patients had no viral hepatitis. Children had folic acid in combination with MTX treatment. Its dose ranged from 0 to 15 mg / week and the average dose was 5.52 ± 0.49 mg / week.

This work complies with ethical standards and was carried out according to the Helsinki Declaration. Statistical analysis was carried out with software package Statistica 7.0. Differences were considered significant at $p < 0.05$.

Results and its discussion

Our findings showed that gastrointestinal complaints frequency in children with JIA reached 47.12%. These findings are consistent with those of large population studies which suggest the frequency of these complaints in children with JIA is from 42% to 58% [10-12]. Some authors attribute the decrease in adherence to MTX therapy due to GIC, even to the refusal of MTX taking (from 15% to 77.3%). Significant proportion of patients experience nausea, vomiting, abdominal pain and loss of appetite, mainly during MTX therapy [10].

Compared with other studies, children with JIA had less frequent abdominal pain (23.08%), loss of appetite (25.00%) and nausea (18.27%). Data on the frequency of complaints of vomiting had the same direction with other authors (8.65%).

There is considerable variability in these data according to the literature. Thus, the frequency of complaints of abdominal pain ranges from 27.9% to 74% [10], nausea associated with MTX - from 28% to 73% [10] and from 36.7 to 91.3 % [12], for vomiting - from 4.8% to 49.3% [10], and from 15% to 43%, [12].

Our findings showed that there is no significant difference in the prevalence of complaints based on the sex of the child, which is also not reflected in modern sources. It is noted that in the general group of patients with JIA, children rarely complained of vomiting ($p < 0.01$), especially girls ($p < 0.01$).

According to our results GIC mostly were common for patients aged 10 to 13 years (55.36%; $p < 0.001$). Younger children complained mostly on abdominal pain and vomiting. Complaints on decreased appetite and nausea were common for older children. The highest number GIC was observed in children who became ill after 15 years old ($p < 0.01$).

At the same time, according to modern literature researchers noted that the average age of children with JIA who felt unwell while taking MTX was 11 years, and the average age of

children who tolerated MTX was 12 years (p = 0.015) [10], which coincides with our data.

It was noted that all surveyed children, whose disease onset age ranged from 15 to 18 years, had gastrointestinal complaints (p <0.01). Almost half of the children with the onset of JIA fewer than 10 years old and one third of the children with JIA onset between 11 and 14 years old complained on abdominal pain, loss of appetite, nausea and vomiting. At the same time, they were dominated by decreased appetite and nausea (p <0.05). Thus, with the debut of JIA under 11 years old, the frequency of complaints of gastrointestinal changes was about 50 percent. Children who fell ill between 11 and 14 years old complained the least, and only a third of them reported gastrointestinal disorders.

In children with JIA, GIC did not depend on the variant of arthritis, the frequency of complaints of nausea and vomiting in children with polyarticular variant of JIA almost coincides with some literature data and is 21% and 11% [12]. The nature of the complaints did not depend on JIA activity and duration, but similar data were not found in the available sources.

Table 1. Frequency of gastrointestinal complaints in children, taking into account gender, age of the child, age of juvenile idiopathic arthritis onset, variant of juvenile idiopathic arthritis, duration of arthritis, degree of JADAS-27 activity, presence of methotrexate in treatment and its regimen,

%

Grouping		n	Abdominal pain	Loss of appetite	Nausea	Vomiting	All gastro intestinal complaints
Gender	boys	42	23,81	26,19	21,43	2,38[1]	57,14
	girls	62	22,58	24,19	16,13	12,90[1]	40,32
Age	<10 y.	14	35,71	7,14[5]	21,43	7,14	57,14
	10–13 y.	56	21,43	33,93[5,6]	19,64	10,71	55,36 [8]
	14–18 y.	34	20,59	17,65[6]	14,71	5,88	29,41[8]
Age of JIA onset	< 3 y.	9	33,33	44,44	22,22	11,11	55,56[9]
	3–5 y.	35	22,86	22,86	11,43[8]	11,43	48,57[9]
	6–10 y.	33	24,24	24,24	24,24	3,03	51,52[9]
	11–14 y.	24	16,67	16,67[6]	16,67	8,33	29,17[9]
	15–18 y.	3	33,33	66,67[6]	66,67[8]	—	100[9]
Variant of JIA	oligo arthritis	42	28,57	28,57	16,67	4,76	57,14
	poly arthritis	53	16,98	26,42	20,75	13,21	41,51
	undifferentiated	9	33,33	—	11,11	—	33,33
Duration of JIA	< 1 y.	11	18,18	27,27	36,36	—	45,45
	1–3 y.	32	25,00	25,00	15,63	12,50	43,75
	> 3 y.	61	22,95	24,59	16,39	8,21	49,18
Disease activity	inactive disease	4	25,00	50,00	50,00	25,00	75,00

according to JADAS-27	low	60	25,00	21,67	20,0	6,67	46,67
	moderate	36	19,44	25,00	11,11	8,33	44,44
	high	4	50,00	50,00	25,00	25	50,00
MTX treatment	not present	25	26,92	26,92	11,54	7,69	44,00
	present	79	21,79	24,36	20,51	8,97	48,10
Dose of MTX, mg/m^2/ week	< 10	5	40,00	60,00[5]	40,00	—	80,00[10]
	10–12,5	34	15,15	9,09 [5]	21,21	3,03	52,94
	12,6–15	33	27,27	33,33	21,21	18,18	54,54
	> 15	7	14,29	28,57	—	—	28,57[10]
All children with JIA		104	23,08 [2]	25,00[3]	18,27[4]	8,65[2,3,4]	47,12

Notes: significant differences of complaints on: vomiting:
1 - p < 0.01 in girls and boys,
2,3,4 - p < 0,01 in comparison with other complaints; decreased appetite in children:
5 - p < 0.001 under the age of 10 and 10 - 13 years, with a dosage of MTX less than 10 and from 10 to 12.5 mg /m2/ week,
6 - p < 0.05 age 10 - 13 years and 14 - 18 years, with the age of JIA onset from 11 to 14 years and from 15 to 18 years;
7 - p <0.05 significant differences of nausea in children with the age of JIA onset from 3 to 5 years and from 15 to 18 years;
8 - p < 0.001; significant differences of gastrointestinal complaints in children aged 10-13 years and 14-18 years;
9 - p <0.01 significant differences of complaints of children with the age of JIA onset from 15 to 18 years;
10 - p < 0.05 significant differences of complaints in children with MTX dosage less than 10 and more than 15 mg / m2 / week.

A large proportion of studies show an importance duration of the disease and the duration of therapy [10-12]. Our results did not reveal significant differences in the frequency of complaints in children with different variants of JIA. According to our studies children had vomiting when JIA duration was more than 1 year. Analysis of the prevalence of changes in gastrointestinal complaints, taking into account the activity of JIA on JADAS-27 did not identify significant differences.

Our findings showed that children with JIA had complaints regardless of the presence of MTX in complex therapy. The dosage regimen was more important: when prescribing MTX at a dose of less than 10 mg / m^2, the frequency of gastrointestinal complaints was significantly higher than when dosing more than 15 mg / m^2 per week ($p < 0.05$). Children who received MTX less than 10 mg / m^2 / week did not complain on vomiting at all, but they complained on decreased appetite ($p < 0.001$). Children who received MTX more than 15 mg / m^2 / week complained only on decreased appetite and abdominal pain.

These findings are consistent with those of large population studies which suggest that children with JIA and intolerance to MTX had average dose 9.8 mg / m^2, while children who tolerated MTX, received it in average dose 10.9 mg / m^2 ($p = 0.002$) [10]. However, children with JIA who did not tolerate MTX, on average, used the drug for 2 years, while children who did not refuse to take MTX, used it for a much shorter period ($p = 0.001$) [10].

Thus, the presence of complaints in children with JIA is an important and clinically significant point to pay attention to when observing these children.

Conclusions

1. Children with JIA had gastrointestinal complaints in 47.12% of cases, most often aged 10–13 years (55.36%; $p < 0.001$), with the JIA onset over 15 years of age ($p < 0.01$).

2. Children under the age of six mostly had abdominal pain and vomiting. Decreased appetite and nausea were common in children over 15 years old. The presence of complaints did not depend on the option, activity and duration of JIA.

3. There was no clear relationship between complaints and MTX intake, but children complained much more often if the dose was less than 10 mg / m2 than in the case of higher dosage ($p < 0.05$).

Comparison of the results with the data available in the literature suggests that the urgent task of clinicians is to more closely monitor gastrointestinal complaints, as only the vomiting

coincided with global studies of gastrointestinal status among other pediatric cohorts of patients with JIA.

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КЛІНІЧНІ ПРОЯВИ ЗМІН З БОКУ ШЛУНКОВО-КИШКОВОГО ТРАКТУ У ДІТЕЙ З ЮВЕНІЛЬНИМ ІДІОПАТИЧНИМ АРТРИТОМ

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Резюме. *Ювенільний ідіопатичний артрит залишається одним із найпоширеніших хронічних запальних ревматичних захворювань дитячого віку. Значна частина пацієнтів відчуває нудоту, блювоту, болі в животі та зниження апетиту на тлі терапії метотрексатом, що може значно ускладнити перебіг захворювання.*

Мета *вивчити клініко-анамнестичні ознаки порушень стану печінки в дітей, з урахуванням особливостей перебігу ювенільного ідіопатичного артриту.*

Матеріали та методи дослідження. *Проаналізовано наявність скарг з боку шлунково-кишкового тракту, а саме скарг на біль у животі, зниження апетиту, нудоту та блювання у 104 дитини, хворих на ювенільний ідіопатичний артрит, які перебували на лікуванні в Державній установі «Інститут охорони здоров'я дітей та підлітків НАМН України».*

Результати. *За результатами дослідження визначено, що у дітей хворих на ювенільний ідіопатичний артрит визначені скарги з боку шлунково-кишкового тракту у 47,12 % випадків. Серед усіх обстежених дітей більшою мірою діти скаржились у віці 10–13 років (55,36 %, $p < 0,001$), та при дебюті захворювання після 15 років (100 %, $p < 0,01$). Для дітей молодшого віку були характерними скарги на біль у животі та блювання, для дітей старшого віку — зниження апетиту та завзята нудота, незалежно від варіанту, активності, тривалості артриту та наявності метотрексату у складі комплексної терапії. Також виявлено, що зазначені скарги спостерігалися частіше при дозі метотрексату менше ніж 10 мг/м^2/поверхні тіла ($p < 0,05$).*

Висновки. *1. Діти, хворі на ювенільний ідіопатичний артрит, мали скарги з боку шлунково-кишкового тракту у 47,12 % випадків. Найчастіше це пацієнти 10–13 років (55,36 %; $p < 0,001$). Найбільш притаманні скарги пацієнтам, які захворіли у віці понад 15 років ($p < 0,01$). 2. Характер скарг відрізнявся та переважно залежав від віку пацієнтів. Діти молодшого віку мали болі в животі та блювання. Для дітей старшого віку були характерні зниження апетиту та нудота. Наявність скарг не залежала від варіанту, активності та тривалості захворювання. 3. Скарги не зумовлювалися наявністю метотрексату у комплексній терапії, але діти значно частіше скаржилися, якщо доза була меншою за 10 мг/м^2, ніж у разі вищого дозування ($p < 0,05$).*

Ключові слова: ювенільний ідіопатичний артрит, метотрексат

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КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ ИЗМЕНЕНИЙ СО СТОРОНЫ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА У ДЕТЕЙ С ЮВЕНИЛЬНЫМ ИДИОПАТИЧЕСКИМ АРТРИТОМ

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Резюме. *Ювенильный идиопатический артрит остается одним из наиболее распространенных хронических воспалительных ревматических заболеваний детского возраста. Значительная часть пациентов испытывает тошноту, рвоту, боли в животе и снижение аппетита на фоне метотрексатом, что может осложнить течение заболевания.*

Цель *изучить клинико-анамнестические признаки нарушений состояния печени у детей с учетом особенностей течения ювенильного идиопатического артрита.*

Материалы и способы исследования. *Проанализировано наличие жалоб со стороны желудочно-кишечного тракта, а именно жалоб на боль в животе, снижение аппетита, тошноту и рвоту у 104 детей, больных ювенильным идиопатическим артритом, которые находились на лечении в Государственном учреждении «Институт здравоохранения детей и подростков НАМН Украины».* ***Результаты.*** *По результатам исследования определено, что у детей больных ювенильным идиопатическим артритом жалобы со стороны желудочно-кишечного тракта встречаются в 47,12% случаев. Среди всех обследованных детей в большей степени дети жаловались в возрасте 10-13 лет (55,36%, p 0,001), и при дебюте заболевания после 15 лет (100%, p 0,01). Для детей младшего возраста были характерны жалобы на боль в животе и рвоту, для детей старшего возраста – на снижение аппетита и упорную тошноту, независимо от варианта, активности, продолжительности артрита и наличия метотрексата в составе комплексной терапии. Также выявлено, что указанные жалобы наблюдались чаще при дозе метотрексата менее 10 мг/м^2/поверхности тела (p 0,05).*

Выводы. *1. Дети, больные ювенильным идиопатическим артритом, имели жалобы со стороны желудочно-кишечного тракта в 47,12% случаев. Чаще это пациенты 10–13 лет (55,36%; p 0,001). Наиболее присущи жалобы пациентам, заболевшим в возрасте более 15 лет (p 0,01). 2. Характер жалоб отличался, и в основном зависел от возраста пациентов. У детей младшего возраста наиболее характерны жалобы на боли в животе и рвоту. Для детей старшего возраста — на снижение аппетита и тошноту. Наличие жалоб не зависело от варианта, активности и длительности артрита. 3. Жалобы не обусловливались наличием метотрексата в комплексной терапии, но дети значительно чаще жаловались, если доза была менее 10 мг/м^2, чем при более высокой дозировке (p < 0,05).*

Ключевые слова: ювенильный идиопатический артрит, метотрексат

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