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Features of Crohn's Disease Depending on the Age of Disease Onset

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Aim: to evaluate the characteristics of Crohn's disease depending on the age of the disease onset in patients observed in a specialized City Center for Inflammatory Bowel Diseases Diagnosis and Treatment.
Materials and methods. We observed 180 patients with an established diagnosis of Crohn's disease for 52 weeks, followed by a retrospective assessment. Patients were divided into three groups depending on the age of the onset of the disease according to the Paris classification (A1, A2, A3). The visits included: the collection of complaints, medical history, objective examination, clinical blood testing; biochemical blood testing (C-reactive protein); fecal calprotectin; ileocolonoscopy. Statistical processing of the obtained data was carried out using Excel, RStudio and the R language; for categorical data, the Pearson chi-square test or Fisher's exact test was used (for 2 × 2 tables with small samples). For categorical and quantitative, the Mann – Whitney *t*-test was used. Student's *t*-test was used to test the equality of means.
Results. The gender distribution and the average duration of the disease were comparable in all groups. At the time of diagnosis, ileocolitis ($p = 0.01$), inflammatory form of Crohn's disease ($p < 0.05$), and the upper gastrointestinal tract involvement ($p < 0.05$) were more frequently detected in group A1. Isolated colonic Crohn's disease predominated in group A3 ($p < 0.001$). No significant difference between the groups in the incidence of extraintestinal manifestations of the disease was found ($p = 0.32$). In group A1, there was a positive correlation between smoking and lack of response to therapy. In group A2, endoscopic remission was observed less frequently among smokers at the end of the study ($p < 0.05$). Anal fissures were noted as the most common perianal disease in all groups. In group A1, there was a positive correlation between clinical, laboratory and endoscopic remission and the absence of perianal disease. At the end of the follow-up, the worsening of endoscopic SES-CD level was observed more frequently in the patients with the onset before 30 years old in group A2 ($p = 0.01$).
Conclusions. Not only pediatric onset, but also the onset of Crohn's disease before the age of 40 is a risk factor for the progression of the disease and its more severe course.
Keywords: Crohn's disease, inflammatory bowel diseases, biological therapy, the age of the onset of Crohn's disease
Conflict of interest: the authors declare that there is no conflict of interest.

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Особенности болезни Крона в зависимости от возраста начала заболевания

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Цель: оценить особенности болезни Крона в зависимости от возраста начала заболевания у пациентов, наблюдающихся в специализированном городском центре диагностики и лечения воспалительных заболеваний кишечника.
Материалы и методы. Мы наблюдали 180 пациентов с установленным диагнозом «болезнь Крона» в течение 52 недель с последующей ретроспективной оценкой. Пациенты были разделены на три группы в зависимости от возраста начала заболевания согласно Парижской классификации (A1, A2, A3). На визитах проводились: сбор жалоб, анамнеза, объективный осмотр, клинический анализ крови; биохимический анализ крови (С-реактивный белок); фекальный кальпротектин; илеоколоноскопия с биопсией; морфологическое исследование биоптатов кишки. Статистическая обработка полученных данных проводилась с использованием программ Excel, RStudio и языка R, для категориальных данных использовались критерий χ^2 Пирсона

или точный тест Фишера (для таблиц 2 × 2 с малыми выборками). Для категориальных и количественных использовался *t*-test Манна — Уитни. Для проверки равенства средних значений использовался *t*-критерий Стьюдента.

Результаты. Распределение по полу и средняя продолжительность болезни были сопоставимы во всех группах. На момент установления диагноза в группе A1 чаще выявлялся илеоколит ($p = 0,01$), воспалительная форма болезни Крона ($p < 0,05$), поражение верхних отделов желудочно-кишечного тракта ($p < 0,05$). В группе A3 преобладало изолированное поражение толстой кишки ($p < 0,001$). Достоверного различия между группами в частоте встречаемости внекишечных проявлений болезни установлено не было ($p = 0,32$). В группе A1 отмечалась положительная корреляция между курением и отсутствием ответа на терапию. В группе A2 среди курильщиков чаще регистрировалось отсутствие эндоскопической ремиссии на момент окончания исследования ($p < 0,05$). По характеру перианального поражения во всех группах отмечалось преобладание анальных трещин. В группе A1 отмечалась положительная корреляция между отсутствием перианального поражения и достижением клинической, лабораторной и эндоскопической ремиссии на момент окончания исследования. В группе A2 ухудшение по данным эндоскопического исследования наблюдалось чаще среди тех пациентов, кто заболел в возрасте до 30 лет ($p = 0,01$).

Выводы. Не только детский возраст, но и начало болезни Крона в возрасте до 40 лет являются фактором риска прогрессирования болезни и более тяжелого ее течения.

Ключевые слова: болезнь Крона, воспалительные заболевания кишечника, генно-инженерная биологическая терапия, возраст начала заболевания

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Introduction

Crohn's disease is a chronic inflammatory disorder of the intestine that leads to progressive gut damage and patient disability. The main aim in managing Crohn's disease is to stop the disease progression. Studying the factors of poor prognosis helps to identify groups of patients for early treatment with biological therapy [1, 2].

Among the recognized factors of poor prognosis are currently listed: the presence of complications of the disease at the time of diagnosis, disease extension [1, 2], male gender [3], the presence of perianal disease [1, 4, 5], young age at the time of diagnosis [6–9] and the need for steroids at the time of diagnosis [5].

Many scientists consider the early onset of the disease as one of the factors of a poor outcome. Some studies have provided evidence that pediatric onset of Crohn's disease is characterized by a more severe disease course and a poor outcome [10, 11], and therefore requires early treatment with biological therapy that changes the natural course of the disease [1]. Some studies suggest that there is no such dependence and a poor prognosis for pediatric onset of Crohn's disease is associated with the duration of the disease [12;13]. Thus, the issue of the influence of the age of onset of Crohn's disease on its course remains controversial [9, 14–16].

Aim: to evaluate the characteristics of Crohn's disease depending on the age of the onset of the disease in patients observed in a specialized City Center for Inflammatory Bowel Diseases Diagnosis and Treatment.

Materials and methods

We examined 180 patients diagnosed with Crohn's disease (CD). The age of the onset of CD was assessed by the date of the patient's initial visit to the doctor with the corresponding clinical symptoms, due to the fact that in 78 % of the cases there was a delay in diagnosis by more than 1 year. Exclusion criteria were isolated upper gastrointestinal tract involvement and ostomy in previous case history.

Patients were divided into three groups depending on the age of the disease onset according to the Paris classification. Group A1 included patients with the onset disease before the age of 17 ($n = 60$), Group A2 — patients with the disease onset between the ages of 18 and 40 ($n = 60$), Group A3 — patients with the disease onset at the age over 40 ($n = 60$). Four hospital visits were carried out over one year (Fig. 1).

The clinical activity of the disease was assessed based on the complaints and the objective examination of the patient; the Harvey — Bradshaw index was used. Laboratory activity of the disease was assessed based on the clinical blood test data and erythrocyte sedimentation rate, C-reactive protein, and fecal calprotectin.

Ileocolonoscopy with SES-CD, Rutgeerts activity indices were used for the assessment of endoscopic disease activity.

The complaints, the objective examination and laboratory examination data were used for safety assessment.

Lifestyle correction included nutritional recommendations, as well as a history of tobacco smoking and its prevention.

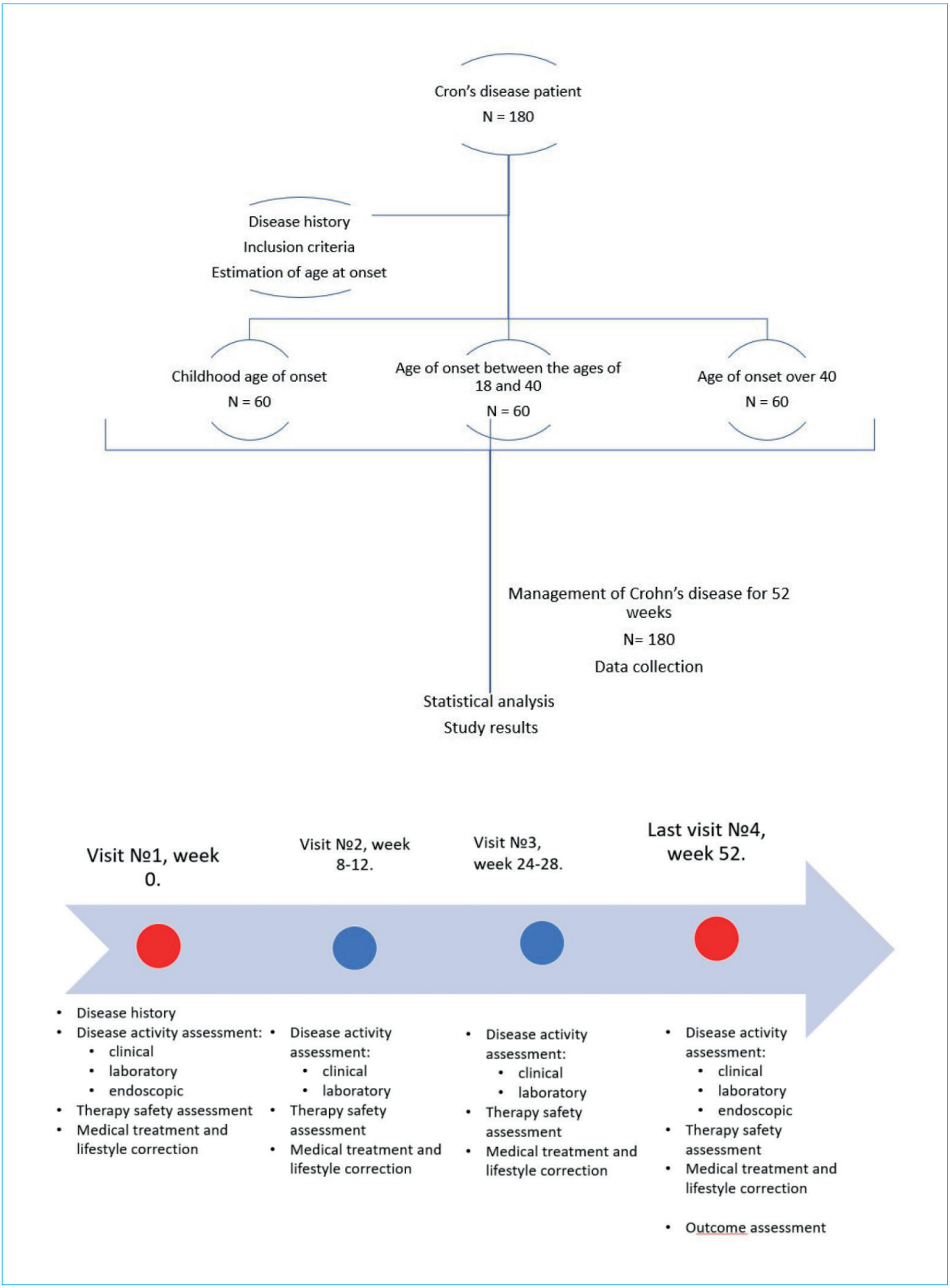

Figure 1. Study design

Рисунок 1. Дизайн исследования

The main target was to achieve clinical, laboratory, and endoscopic remission. Clinical remission was regarded as the absence of abdominal pain and the normalization of stool frequency and consistency. Laboratory remission was regarded as the normalization of laboratory parameters (the levels of leukocytes, hemoglobin, platelets, erythrocyte sedimentation rate, C-reactive protein, the level of fecal calprotectin). Endoscopic remission was regarded as the absence of ulcerative lesions of the mucous membrane, SES-CD ≤ 3 points, Rutgeerts i0.

Statistical processing of the obtained data was carried out using Excel, RStudio and the R language; for categorical data, the Pearson chi-square test or Fisher's exact test was used (for 2 × 2 tables with small samples). For categorical and quantitative, the Mann — Whitney *t*-test was used. Student's *t*-test was used to test the equality of means.

Results

The characteristics of patients at the time of disease onset and diagnosis are presented in Table 1.

Table 1. Characteristics of patients at the time of disease onset and upon diagnosis of Crohn's disease
Таблица 1. Характеристика больных на момент начала заболевания и при постановке диагноза «болезнь Крона»

Parameters **Признаки**	**Group A1** **Группа А1** **(*n* = 60)**	**Group A2** **Группа А2** **(*n* = 60)**	**Group A3** **Группа А3** **(*n* = 60)**
Males / *Females, n* Мужской пол / *Женский пол, n*	31/29	32/28	21/39
Age at onset of disease *Возраст на момент начала заболевания*	14.5 yrs ± 2 yrs 1 m *14,5 года* *± 2 года 1 мес.*	29.2 yrs ± 6 yrs 1 m *29,2 года* *± 6 лет 1 мес.*	52 yrs ± 8 yrs 6 m *52 года* *± 8 лет и 6 мес.*
Diagnosis delay *Время до постановки диагноза*	10.1 months *10,1 мес.*	36.5 months *36,5 мес.*	31.8 months *31,8 мес.*
Classification of Crohn's disease at the time of diagnosis (Paris classification 2011) *Классификация болезни Крона при постановке диагноза (Парижская классификация 2011 г.)*			
localization / *локализация*:			
- L1 (terminal ileitis / *терминальный илеит*)	12	16	10
- L2 (colitis / *колит*)	15	24	36
- L3 (ileocolitis / *илеоколит*)	33	21	14
- L4 (upper gastrointestinal tract involvement / *поражение верхнего отдела ЖКТ*)	11	4	3
form / *форма*:			
- B1 (inflammatory / *воспалительная*)	55	42	47
- B2 (stricturing / *стриктурирующая*)	2	7	2
- B3 (penetrating / *пенетрирующая*)	2	6	3
- B2B3 (penetrating with strictures / *пенетрирующая со стриктурами*)	1	5	8
- *p* (perianal / *перианальная*)	16	13	10
Medications at the time of diagnosis: *Терапия, начатая при постановке диагноза:*			
- no therapy / *без терапии*	0	2	0
- immunosupressants (azathioprine/metotrexat) - *иммуносупрессоры (азатиоприн/метотрексат)*	28	14	17
- 5-ASA / *5-аминосалициловая кислота*	57	58	60
- GIBT (Infliximab/Adalimumab/Vedolizumab) - *ГИБТ (Инфликсимаб/Адалимумаб/Ведолизумаб)*	9	2	0
- glucocorticosteroids / *глюкокортикостероиды*	32	20	21

Note: GIBT — genetically engineered biological therapy.
Примечание: ГИБТ — генно-инженерная биологическая терапия.

Gender distribution was comparable in all groups, albeit in Group A3 there was a slight predominance of females ($n = 39$, $p = 0.06$).

The most common complaints at diagnosis in all groups were frequent diarrhea, abdominal pain, and fever. Complaints of weight loss, general weakness and fever prevailed in Group A1 compared to the others, but no significant differences were identified.

The localization of CD at diagnosis in Group A1 was significantly more frequently represented by ileocolitis (L3) compared to the other groups ($p = 0.01$). In turn, in Group A3, isolated involvement of the colon significantly prevailed compared to the other groups ($p < 0.001$). Upper gastrointestinal tract involvement was significantly more common in Group A1 than in the other groups ($p < 0.05$). The inflammatory behavior of CD (B1) significantly predominated in Group A1 ($p < 0.05$). Perianal disease was also more common in Group A1, but there was no significant difference between the groups ($p = 0.27$).

Steroids use at the time of diagnosis was highest among patients in Group A1 ($n = 32$ vs. $n = 20$ and $n = 21$ in the other groups). Moreover, a positive correlation with laboratory remission at the end of study was noted among those patients of Group A1 who did not receive oral steroids at the time of diagnosis, while for the other two groups such a correlation was not found (Fig. 2).

There was a significant difference in the time from CD onset to biologic therapy start: in Group A1 it was 24 months on average, in Group A2 — 77 months, in Group A3 — 58 months ($p < 0.05$) (Fig. 3).

The most frequent indications for biological treatment were in Group A1 the ineffectiveness of immunosuppressants (40 % of the prescribed cases), complications of the disease (33 %) and steroid dependence (28 %), in Group A2 — immunosuppressants intolerance (55 %), their ineffectiveness (48 %), and steroid dependence (42 %); in Group A3 — immunosuppressants intolerance (75 %), steroid dependence (64 %) and immunosuppressants

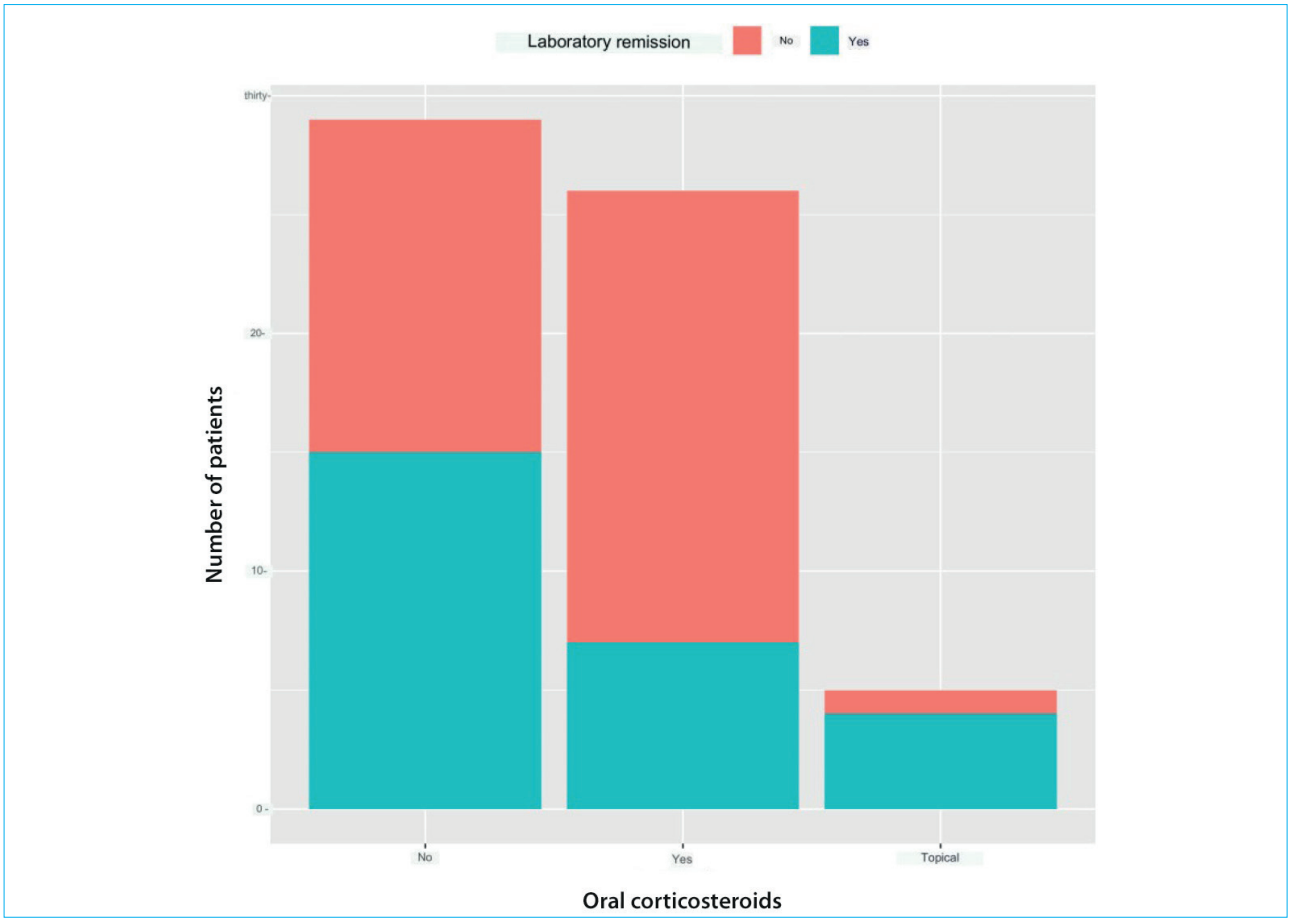

Figure 2. Association of laboratory remission at week 52 with the need for glucocorticosteroids at the time of diagnosis

Рисунок 2. Связь лабораторной ремиссии на 52-й неделе с потребностью в назначении глюкокортикостероидов во время постановки диагноза

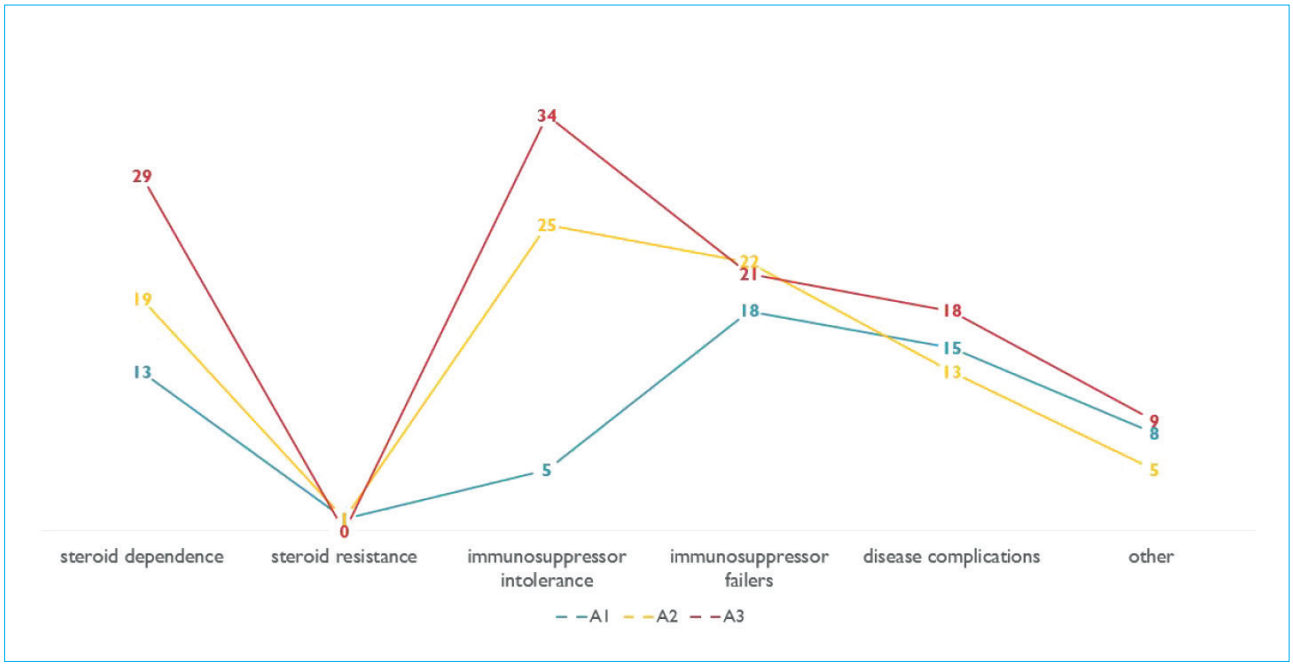

Figure 3. Indications for prescribing genetic engineering biological therapy

Рисунок 3. Показания для назначения генно-инженерной биологической терапии

ineffectiveness (45 %). The duration of biological therapy until the first study visit in Group A1 was 35.1 months on average, in group A2 — 11.5 months, and in Group A3 — 14 months.

CD duration at the time of the first study visit was comparable in the groups with the onset between the ages of 18 and 40 and over 40 years old and was 6 years 6 months and 6 years 1 month, respectively; and in the group with pediatric onset the average duration of the disease was significantly shorter and amounted to 4 years 7 months ($p < 0.05$) (Table 2).

The number of patients who continued to smoke was higher in the group with the onset of the disease between 18 and 40 years old. At the same time, the number of former smokers prevailed in Group A3 and amounted to 41.6 % of patients, but no statistically significant correlations with the outcome of the disease were obtained in Group A3.

In Group A1 there was a positive correlation between smoking and lack of response to therapy. Thus, lack of response to therapy, including unstable improvement, was noted more often among those who smoked during the study period (Fig. 4).

The absence of endoscopic remission was more often recorded at the final visit in Group A2 according to ileocolonoscopy in patients who continued to smoke ($p = 0.04$) (Fig. 5).

There was an increased number of complicated behavior in all groups at the first visit, while a significant difference remained in the number of cases of the inflammatory behaviour of the disease between Groups A1 and A2 ($p < 0.05$). There were no changes in the number of complications during the study period from the first to the fourth visit.

A change in the extent of disease was recorded in only one patient from Group A1 (L1 to L3) and one patient from Group A2 (L2 to L3) during study period.

There was a relationship between the endoscopic progression of CD (larger ulcer size or larger area of mucosal lesions) and the onset of the disease at a younger age in Group A2 ($p = 0.01$) (Fig. 6).

There was no significant difference between the groups in the incidence of extraintestinal manifestations of the disease ($p = 0.32$) although they were most often recorded in Group A1. The combination of several extraintestinal manifestations was more common in the first and third groups, in 24 and 40 % of cases, respectively. Aphthous stomatitis occurred more frequently in Group A1 (48 %). Peripheral spondyloarthritis was most common in Group A3 (54 %). In group A2, extraintestinal manifestations were less common and no predominance of any of them was detected.

Anal fissures were the most common perianal complication: 65 % of patients — in Group A1, 71 % — in Group A2, and 85 % — in Group A3 (Table 4). We obtained a significant difference in the prevalence of perianal lesions in Group A1 in contrast to Group A3 at the first visit ($p = 0.02$).

Table 2. Characteristics of patients at the first visit

Таблица 2. Характеристика больных на первом визите

Parameters ***Признаки***	**Group A1** ***Группа А1*** **(*n* = 60)**	**Group A2** ***Группа А2*** **(*n* = 60)**	**Group A3** ***Группа А3*** **(*n* = 60)**
Duration of the disease *Продолжительность болезни*	4 yrs 7 months ± 3 yrs 7 months *4 года 7 мес. ± 3 года 7 мес.*	6 yrs 6 months ± 6 yrs 5 months *6 лет 6 мес. ± 6 лет 5 мес.*	6 yrs 2 months ± 4 yrs 9 months *6 лет 2 мес. ± 4 года 9 мес.*
Smoking / *Статус курения:*			
- current smoker / *курит*	5	9	6
- never smoked / *никогда не курил*	44	37	29
- former smoker / *курил ранее, бросил*	1	14	25
Classification of Crohn's disease at the time of diagnosis (Paris classification 2011) *Классификация болезни Крона на момент первого визита (Парижская классификация 2011 г.)*			
localization /*локализация*:			
- L1 (terminal ileitis / *терминальный илеит*)	8	14	8
- L2 (colitis / *колит*)	4	14	29
- L3 (ileocolitis / *илеоколит*)	48	32	23
- L4 (upper gastrointestinal tract involvement) / *поражение верхнего отдела ЖКТ*	11	6	6
form / *форма*:			
- B1 (inflammatory / *воспалительная*)	45	34	39
- B2 (stricturing / *стриктурирующая*)	6	11	9
- B3 (penetrating / *пенетрирующая*)	6	5	2
- B2B3 (penetrating with strictures / *пенетрирующая со стриктурами)*	3	10	10
- *p* (perianal / *перианальная*)	26	21	14
Medication at the first visit: *Терапия на момент первого визита:*			
- no therapy / *без терапии*	3	6	2
- immunosupressants / *иммуносупрессоры*	13	18	12
- 5-ASA / *5-аминосалициловая кислота*	20	27	25
- tumor necrosis factor-α inhibitors (monotherapy)/ *ингибиторы фактора некроза опухоли- (монотерапия)*	19	17	20
- tumor necrosis factor-α inhibitors + immunosuppressants / *ингибиторы фактора некроза опухоли- + иммуносупрессоры*	20	8	6
- anti-integrin therapy / *антиинтегриновая терапия*	0	0	4
- anti-integrin therapy + immunosuppressants / *антиинтегриновая терапия + иммуносупрессоры*	1	2	2
- glucocorticosteroids, of which (glucocorticosteroids + immunosuppressants and/or + GIBT) / *глюкокортикостероиды, из них (глюкокортикостероиды + иммуно-супрессоры и/или + ГИБТ)*	3 (3)	11 (5)	7 (6)

The need for surgical treatment for perianal complications was numerically highest in Group A1 (46 %). Interestingly, not a single patient from Group A3 was operated on again. At the end of the study, endoscopic remission in patients who had perianal disease was recorded in 31 % of patients in Group A1, in 43 % — in Group A2, and in 50 % — in Group A3. In Group A1, there was a positive correlation between clinical, laboratory and endoscopic remission and the absence of perianal lesions.

At the end of study, clinical, laboratory and endoscopic remission was observed in 40 % of patients in Group A1, in 41.6 % — in Group A2, and in 46 % — in Group A3. These patients had similar clinical findings. In those patients who received

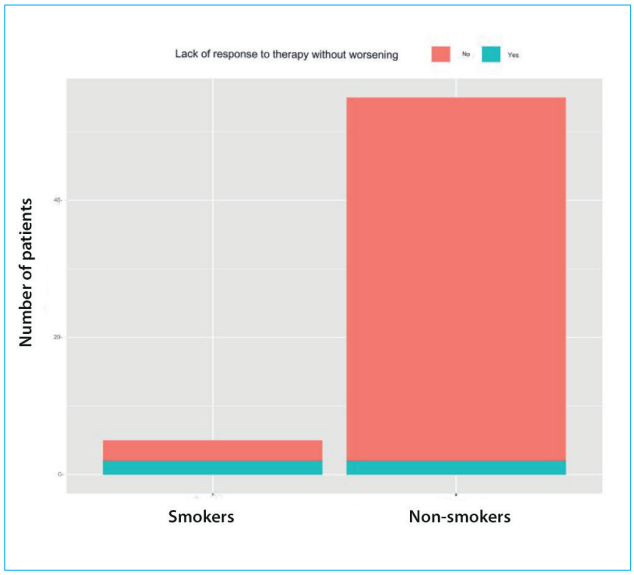

Figure 4. Relationship between smoking status and response to treatment at the fourth visit

Рисунок 4. Зависимость между статусом курения и ответом на терапию на четвертом визите

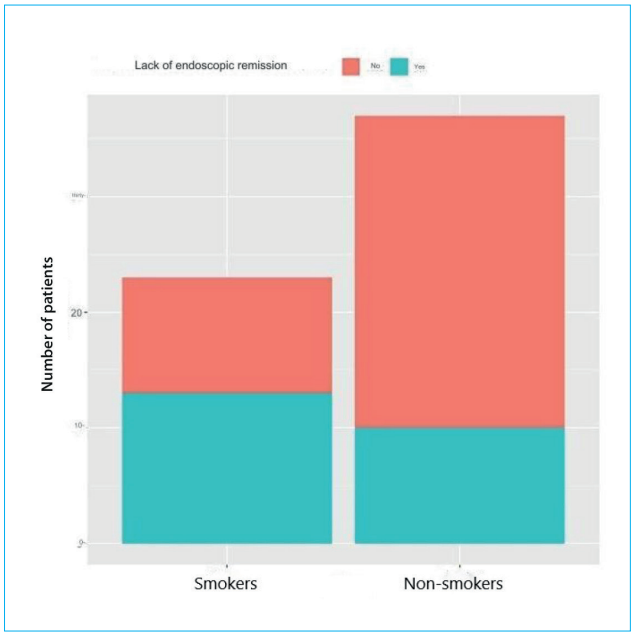

Figure 5. Relationship between smoking status and endoscopic outcome at the fourth visit

Рисунок 5. Зависимость между статусом курения и эндоскопическим исходом на четвертом визите

biological therapy, the clinical and laboratory response to the induction course of the drug was recorded. They had inflammatory behaviour of the disease. Deep ulceration didn't record in most cases according to endoscopy. In those patients who received traditional therapy, inflammatory behaviour of the disease was recorded. Among them, the following were not recorded: steroid dependence, deep ulcerations of the mucous membrane according to endoscopy, and perianal disease.

Discussion

Our study confirmed the predominance of colonic Crohn's disease localization in patients whose age of onset was over 40 years old, which corresponds to the data obtained by other authors [8, 17, 18]. In patients who had pediatric onset of Crohn's disease, an extensive lesion (ileocolitis) predominates, which is consistent with the data obtained [19]. The incidence of colonic localization of Crohn's disease in patients over the age of 40 years old in our population was similar to the European population (58 % vs. to 60 % in patients in Northern France) [8]. It is known that colon lesions are more common among female patients [20, 21]. This may explain the predominance of colonic localization in Group A3.

Perianal disease in general, and severe forms of perianal disease in particular, are more common in patients with pediatric onset and are associated

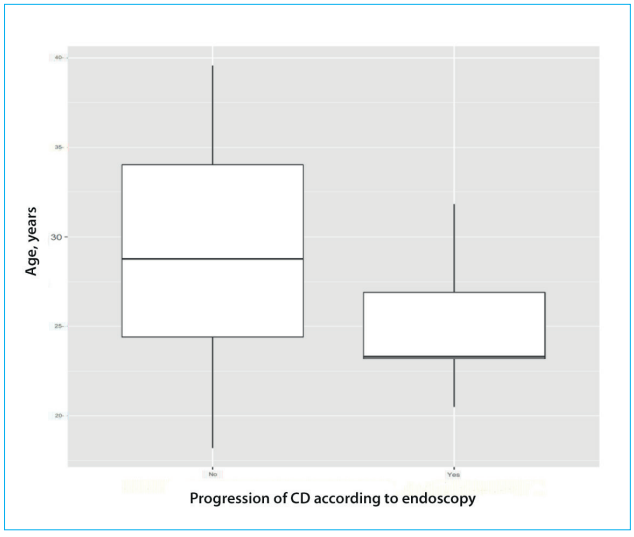

Figure 6. Relationship between age of onset and progression of Crohn's disease as determined by endoscopy at the fourth visit

Рисунок 6. Зависимость между возрастом начала болезни и прогрессированием болезни Крона по данным эндоскопии на четвертом визите

with a worse prognosis and a greater need for intensified therapy [22]. Moreover, the presence of perianal disease is considered a more significant factor in poor prognosis than the age of the disease onset [22]. We confirmed that perianal involvement is an independent factor for poor prognosis in

Table 3. Extraintestinal manifestations of the disease at the time of the first follow-up visit

Таблица 3. Внекишечные проявления болезни на момент первого визита в рамках наблюдения

Extraintestinal manifestations *Внекишечные проявления*	**Group A1** *Группа А1* **(*n* = 60)**	**Group A2** *Группа А2* **(*n* = 60)**	**Group A3** *Группа А3* **(*n* = 60)**
Total patients with EIM / *Всего пациентов с ВКП*	29	10	22
Patients with two or more EIM / *Пациенты с двумя и более ВКП*	7	3	9
Skin involvement / *Поражение кожи*:			
- erythema nodosum / *узловатая эритема*	4	3	3
- pyoderma gangrenosum / *гангренозная пиодермия*	1	0	1
Damage to the mucous membranes (aphthous stomatitis) *Поражение слизистых (афтозный стоматит)*	14	3	5
Eye involvement / *Поражение глаз*:			
- uveitis / *увеит*	2	1	0
- iridocyclitis / *иридоциклит*	0	1	3
- episcleritis / *эписклерит*	1	1	0
Arthropathies / *Артропатии*:			
- peripheral spondyloarthritis / *периферический спондилоартрит*	10	1	12
- axial spondyloarthritis / *осевой спондилоартрит*	0	2	4
Ankylosing spondylitis (sacroiliitis) *Анкилозирующий спондилит (сакроилеит)*	0	2	5
Primary sclerosing cholangitis *Первичный склерозирующий холангит*	2	1	0
Psoriasis / *Псориаз*	2	3	4
Osteoporosis / *Остеопороз*	1	0	4

Note: EIM — extraintestinal manifestations.

Примечание: ВКП — внекишечные проявления.

Table 4. Perianal lesions in groups at the first visit to the Center (%)

Таблица 4. Перианальные поражения в группах при первом визите в центр (%)

The nature of the perianal lesion *Характер перианального поражения*	**Group A1** *Группа А1* **(*n* = 26)**	**Group A2** *Группа А2* **(*n* = 21)**	**Group A3** *Группа А3* **(*n* = 14)**
Anal fissures / *Анальные трещины*	65	71	85
Acute paraproctitis / *Острый парапроктит*	27	24	21
Simple perianal fistula / *Простой перианальный свищ*	27	14	21
Complex perianal fistula / *Сложный перианальный свищ*	27	19	7
Operated (repeatedly) / *Оперированы (повторно)*	46 (19)	42 (9)	28 (0)

patients with pediatric onset. In all three groups, not a single patient who received traditional therapy and was in remission at the end of the study had perianal disease. An association between perianal lesions and the risk of intestinal surgery was not found, regardless of the presence of perianal lesions at the time of the disease onset or its occurrence during the course of the disease, although similar findings have been described previously [23, 24]. H. Wang et al. [23] also obtained evidence that perianal lesions occurring in childhood are more severe, while perianal lesions occurring in adulthood are more often a predictor of severe intestinal damage [23]. P. Mortreux et al. [25] analyzed a cohort of patients with the onset of the disease in the childhood and revealed a high incidence of anal fissures, while extensive endoscopic lesions predominated in such patients (colitis, ileocolitis and upper gastrointestinal involvement). This is consistent with our data obtained in patients with pediatric onset. According to our data, patients with the age of onset over 40 years old had a milder nature of perianal lesions and less need for surgical treatment than patients with the age of onset under 18 years. We did not obtain a significant difference in the prevalence of extraintestinal manifestations frequency in patients depending on the age of onset of the disease; in

addition, extraintestinal manifestations predominated in the group with the onset of Crohn's disease in the childhood, and M. Calafat et al. [21] obtained a significant predominance of the presence of extraintestinal manifestations in the elderly [21]. Extensive damage to the gastrointestinal tract in patients with pediatric onset, as well as the involvement of the upper gastrointestinal tract, dictates earlier biologic treatment in order to prevent the development of complications of the disease that require intestinal surgery [19].

An important circumstance was that the duration of the disease in the group with pediatric onset was shorter (Group A1 — 4.7; Group A2 — 6.6; Group A3 — 6.2 years), since it is known that over time the disease can progress with the development of complications [26]. According to studies in the European population, over the first five years, approximately 34 % of patients develop complications of Crohn's disease [27, 28], which is consistent with our data. The pediatric onset of the disease as a risk factor for its progression [29] is confirmed by our retrospective assessment, during which the development of complications was most common in patients with pediatric onset of Crohn's disease. There was a significant predominance of the inflammatory behavior in patients with pediatric onset at diagnosis ($p < 0.05$), which we associate with a significant difference in the delay in diagnosis in patients with the onset of the disease over 18 years old ($p < 0.01$). At the final study visit (week 52), not a single change in the disease behavior was recorded, which indicates adequate management tactics and timely prescription and therapy correction.

The number of stricturing complications of the disease (B2 and B2B3) was comparable in groups with the onset of the disease over 18 years and was greater than in the group with pediatric onset ($p = 0.04$). This may be explained by earlier biologic treatment in the pediatric onset group. S.B. Yang et al. [30] showed that the age of onset over 40 years and the disease duration of more than 5 years lead to the risk of developing stricturing complications, while the average age of the patients with stricturing complications was 37.6 ± 15 years [30]. And in a study by M. Calafat et al. [21] the incidence of complications was the same as in the group of patients with an earlier onset of an inflammatory bowel disease [21]. Stricturing complications of Crohn's disease are an urgent and significant problem, which is associated with the lack of classifications of the fibrosis degree and recommendations for its management, therefore, at present, fibrosis of intestinal tissue most often leads to the need for surgery and often to the patient's disability [31]. Inflammation in Crohn's disease can also lead to the formation of inflammatory stenosis, and, accordingly, such stenosis can regress with adequate anti-inflammatory therapy. At the same time, there is no unambiguous data on the moment of the onset of tissue fibrosis, and fibrosis often accompanies inflammation. Currently, there are no drugs that can effectively stop or reduce fibrosis in the gastrointestinal tube [32]. When studying the physiology of fibrosis, several interesting facts were discovered. Thus, the increasing age was a factor in the functional heterogeneity of fibroblasts in mice. Old mice showed variability in the rate of wound healing [33]. Bleomycin-induced pulmonary fibrosis resolved spontaneously in young mice, while in old mice it remained irreversible. The mechanisms underlying this are associated with changes in collagen metabolism during aging, as well as changes in the cytokine 'composition' of wounds during healing [34]. Also, we know about the connection between the human microbiome and the process of fibrosis. It has been found that certain microbial populations are able to influence the progression of fibrosis [35]. It is now known that the human microbiome is influenced by many factors, one of which is the age of the individual. It is possible that the physiology of intestinal fibrosis differs between younger and older patients with Crohn's disease, which may account for differences in the incidence of stricturing complications in children and adults, although scientists more often attribute this difference to the delay in diagnosis in adults as opposed to children [23, 36].

In a study by H.J. Kim et al. [37] on patients with pediatric onset, a family history of Grade 1 inflammatory bowel disease, isolated ileal involvement at diagnosis, and positive antibody titers against *Saccharomyces cerevisiae* were associated with the evolution of the disease course. Early treatment with biological agents significantly reduced disease progression. This study suggests that early aggressive therapy should be considered in children with inflammatory Crohn's disease and risk factors for disease progression to improve long-term outcomes [37].

Smoking is an independent factor for poor outcome [38]. We have also confirmed this for groups with the disease onset before 40 years old. Such data was not obtained for patients with the age of onset over 40 years.

In our cohort of patients, immunosuppressants intolerance and steroid dependence among patients treated with biologic agents were highest in the group with the disease onset age over 40 years, which is consistent with previously published data [39, 40], while in some previous studies such a difference was not noticed [17, 18].

It is known that among the complaints presented by patients, the most common are complaints of diarrhea, abdominal pain and weight loss [41]. We did not obtain a significant difference between the complaints that patients presented depending on the age of onset of the disease, despite the fact that there were significant differences between the groups in the location and behavior of the disease. Also, no differences in the clinical features of the disease are noted in the literature [13]. O.B. Shchukina [42] showed that a frequently identified symptom was general weakness, in 37 % of patients, regardless of the disease behavior. According to our data, most often complaints of general weakness were made by patients with pediatric onset (56 %), 35 % of patients who became ill at the age of 18–40 years, and 21 % of patients with the onset at over 40 years old (in total, 37 % of patients).

Mucosal healing in Crohn's disease is one of the therapy targets, as it improves the prognosis [43]. There is evidence that the presence of deep ulceration according to ileocolonoscopy is a risk factor for colectomy, which can be considered as a predictor of poor outcome [44]. According to N. Coelho-Prabhu et al. [45], deep ulceration and the size of the ulcers were not a predictor of the lack of mucosal healing, while they were precisely the localization of ulcers in the rectum and terminal ileum [45]. Similar data were obtained by P. Rivière et al. [46]. In our study, we did not find a connection between the presence of deep ulceration according to ileocolonoscopy and/or its localization and the absence of endoscopic remission within a year.

Conclusion

Pediatric onset of Crohn's disease is characterized by more extensive gastrointestinal lesions and more severe perianal lesions, which entails the need for more frequent and earlier treatment with biological agents in order to prevent the development of disease complications.

Crohn's disease with the onset at over 40 years old is characterized by a more frequent localization in the colon, which requires a more thorough differential diagnosis with ulcerative colitis in order to minimize delay in diagnosis and timely initiation of adequate therapy.

The onset of Crohn's disease before the age of 40 years should be considered as a factor of poor outcome.

Smoking should be considered as a risk factor for disease progression, especially in patients with the onset before the age of 40 years.

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