

Clinical-anamnestic characteristics and quality of life in patients with the Cajal subtype of chronic slow-transit constipation

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The Cajal subtype of chronic slow-transit constipation (CSTC) is associated with Cajal cell deficiency and is considered the most resistant to conservative therapy. Its diagnosis requires histological analysis of all layers of the intestinal wall, which involves invasiveness and carries the risk of complications. Therefore, the clinical phenotype of this subtype remains insufficiently studied.

OBJECTIVE – to evaluate the clinical-anamnestic characteristics and quality of life in patients with the Cajal subtype of chronic slow-transit constipation following colectomy.

MATERIALS AND METHODS. Over the past 12 years, the Cajal histological subtype of CSTC was diagnosed in 21 patients after colectomy (group O). The comparison group included 70 patients of similar age and sex who did not exhibit signs of CSTC (group R). The study groups did not differ significantly regarding gender, mean age, or body mass index. Clinical-anamnestic data and quality of life were assessed using the PAC-QOL scale in both groups.

RESULTS. Women predominated in both groups: 20 (95.2%) in the main group O and 65 (92.9%) in group R. The mean age was 33.9 ± 8.7 years in group O, compared to 41.5 years in group R. The clinical phenotype of patients with the Cajal subtype who required surgical treatment was characterized by early disease onset at a young age (8.67 ± 5.08 years), a high mean disease duration at presentation (25.24 ± 11.18 years; range 3–51), and genetic predisposition, with a positive family history in first-degree relatives in 50.5% of cases. These patients exhibited prolonged intervals between bowel movements (mean 12.2 ± 4.3 days) and lack of response to conservative therapy. Stool types 1 and 2 on the Wexner scale were observed in 71.4% and 28.6% of patients, respectively. Most patients required manual assistance during defecation (95.2%) and experienced pronounced pain syndrome (visual analog scale 2.8 ± 1.3). Quality of life, as measured by the PAC-QOL scale, showed a significant decline in group O compared to group R across all parameters. Physical discomfort worsened by 2.72 times (3.24 ± 0.44 vs. 1.19 ± 0.29); psychosocial discomfort by 2.19 times (1.84 ± 0.58 vs. 0.84 ± 0.18); anxiety by 2.66 times (2.05 ± 0.24 vs. 0.77 ± 0.24); satisfaction by 2.88 times (2.48 ± 0.59 vs. 0.86 ± 0.28); and the PAC-QOL score by 2.57 times (2.24 ± 0.25 vs. 0.87 ± 0.12), with $p < 0.05$ for all comparisons.

CONCLUSIONS. Our findings confirm the presence of severe clinical and functional disorders in patients with the Cajal subtype, identifying them as potential candidates for surgical treatment.

KEYWORDS

chronic slow transit constipation, Cajal subtype, quality of life, PAC-QOL scale.

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Chronic constipation remains a significant medical and social problem. Recent reviews indicate that the prevalence of chronic idiopathic constipation in the general population is approximately 14%, with higher rates observed in women and elderly patients [6, 16, 18]. This condition is associated with increased

physical and psychosocial discomfort, imposes a substantial burden on healthcare systems, and significantly affects patients' quality of life [2, 5, 6, 15].

Morphological studies classify slow-transit constipation (CSTC) into four main histological subtypes: neuropathic, myopathic, histologically intact,

and the «Cajal» subtype. The latter is characterized by a reduction in the number of interstitial cells of Cajal (ICCs), which serve as the intestinal «pacemakers» [12]. ICCs generate and propagate electrical «slow waves» essential for coordinating peristalsis, and their deficit is associated with severe colonic hypomotility [18].

The clinical features of chronic constipation, specifically slow-transit constipation (STC), are characterized by prolonged colonic transit time and a significant reduction in coordinated colonic motility [1]. CSTC affects 2–4% of the general population and is often refractory to standard therapeutic approaches, resulting in a high functional burden [18].

Despite growing attention to the histological classification of slow-transit constipation, modern literature lacks comprehensive studies describing the clinical-anamnestic and morphological characteristics of patients based on their histological subtype [11]. This gap is primarily due to the challenges in verification, which requires histological analysis of the full thickness of the colonic wall. Particular attention should be paid to the clinical features of the Cajal subtype, as it tends to respond poorly to conservative treatment and may be a suitable candidate for surgery [7].

OBJECTIVE – to evaluate the clinical-anamnestic characteristics and quality of life in patients with the Cajal subtype of chronic slow-transit constipation following colectomy.

Materials and methods

Over a 12-year period, the Cajal histological subtype of CSTC was diagnosed in 21 patients after colectomy [7]. This allowed for a retrospective analysis of the clinical-anamnestic features in patients with the Cajal subtype, supporting its consideration as a potentially distinct clinical form. These patients were included in the main group (Group O). The comparison group included 70 patients of similar age and sex who showed no signs of CSTC (reference group – R). The study groups did not differ significantly regarding gender, mean age, or body mass index. In both groups, females predominated: 20 (95.2%) in the main group O and 65 (92.9%) in the reference group R, $p = 0.486$. The Rome IV criteria were used to diagnose CSTC [3].

Inclusion Criteria

- Age over 18 years.
- CSTC that does not respond or poorly respond to modern conservative treatment methods for at least 6 months.
- Low quality of life (QoL).
- Consent to undergo surgical treatment.
- Consent to complete a QoL questionnaire.

Exclusion Criteria

- Age under 18 years.
- Severe comorbidities.
- Presence of mental disorders.
- Pregnancy.
- Oncological diseases.
- Harmful habits.
- Refusal to complete the QoL questionnaire.
- Proctogenic constipation.
- Irritable bowel syndrome and/or secondary constipation or constipation with a specific etiology (associated with an underlying condition).
- Drug-induced constipation.

Histological and immunological examinations

Samples were collected from various sections of the gastrointestinal tract, including the appendix, ileum, cecum, colon, and sigmoid colon. For our study, samples were taken from all sections of the colon and appendix, including at least three full-thickness sections from the transverse and longitudinal projections, each approximately 2 cm in length. The tissue specimens were fixed in 10% buffered formalin, wired in alcohol, and embedded in paraffin. Serial sections were stained with hematoxylin-eosin. Additionally, an immunohistochemical study was performed on the paraffin blocks using the Polyclonal Ra a-Hu CD 117 (c-kit) antibody (DAKO, Denmark) to detect Cajal cells via the imaging En-Vision™ FLEX System.

Pathohistological study

Microscopic examination was carried out using an Olympus CX23 (Japan) microscope with a nozzle. Morphometric measurements were performed using Olympus Stream (Japan) software. The histological examination focused on evaluating the intestinal wall structure, including the architectonics of glands and the cellular stroma composition within the mucous membrane. Parameters evaluated were total muscle layer thickness, the ratio of the thickness of different layers and the number of layers, the presence of lymphoid cell infiltration, the presence or absence of cytoplasmic inclusions in smooth myocytes, and their relative size. Meissner's plexuses were identified between the outer and inner muscle layers according to typical histological features. The glial cells were determined by their size, the presence of large vesicular nuclei, and Nissl substance. Their approximate number was calculated, and additional characteristics, including the presence or absence of dystrophic changes and lymphoid infiltrates, were assessed [12].

Quality of Life Assessment

The quality of life was evaluated using the disease-specific Patient Assessment of Constipation – Quality

of Life (PAC-QOL) questionnaire, developed and validated by Marquis et al. [14] in 2005. The questionnaire includes 28 items grouped into 4 subscales:

- Worries and concerns (11 items)
- Physical discomfort (4 items)
- Psychosocial discomfort (8 items)
- Satisfaction with treatment (5 items).

Each item is assessed using a 5-point Likert scale, ranging from 0 (not at all/never) to 4 (very much/all the time), reflecting the patient's experience over the previous two-week period. A higher score indicates a worse QoL due to constipation. Total PAC-QOL scores and subscale scores were calculated according to the original PAC-QOL documentation for each patient [14]. QoL was assessed before surgery and one year after surgery.

Before visiting the clinic, all patients had been undergoing conservative therapy, which gradually became less effective over time. The treatment involved a high-fiber diet ($n = 21$, 100%), pharmacological agents ($n = 21$, 100.0%), and cleansing enemas ($n = 21$, 100%).

21 (100%) patients underwent colectomy with low rectal resection.

The impact of the histological subtype of the colonic wall on the clinical course in patients with the Cajal subtype of CSTC was assessed retrospectively. This was done by comparing the histological findings of resected colonic specimens obtained after colectomy with preoperative questionnaire data and medical history.

Clinical characteristics of patients with the Cajal subtype of CSTC were analyzed in comparison with those of the reference group.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics, version 22. Descriptive statistics were calculated. Data normality was assessed using the Shapiro-Wilk test. Mean values were presented as $M \pm SD$. Categorical data were expressed as counts (%). The comparison of mean values for quantitative variables was performed using the Wilcoxon-Mann-Whitney. Comparisons of relative frequencies were performed using Pearson's chi-square test. The null hypothesis of equality of variables was rejected at $p < 0.05$.

Results

Women predominated in both groups: 20 (95.2%) in group O and 65 (92.9%) in group R. The mean age was 33.9 ± 8.7 years in group O, while in group R it was 41.5 years. The average age at disease onset in group O was 8.67 ± 5.08 years. The body mass index

(BMI) was 20.395 ± 2.29 kg/m² in group O and 22.2 ± 2.29 kg/m² in group R, with no statistically significant difference between the groups, $p < 0.05$.

The mean disease duration in group O was 25.24 ± 11.18 years (range: 3–51 years). Stool consistency assessed by the Wexner scale in group O respondents was type 1 in 71.4% and type 2 in 28.6%, whereas in the reference group R, stool types 4, 5, and 3 were observed in 54 (77.1%), 8 (11.4%), and 8 (11.4%) patients, respectively. The average interval between bowel movements in group O was 12.2 ± 4.3 days, whereas patients in group R had daily bowel movements.

A positive family history of chronic slow-transit constipation was observed in 50.5% of patients with the Cajal subtype in the first degree relatives. Manual assistance was required in 20 patients (95.2%) in group O, whereas manual assistance wasn't required in group R.

The mean intensity of abdominal pain, measured by the visual analog scale (VAS) from 0 to 10, was 2.8 ± 1.3 (range: 1 to 5) in group O respondents, with 14 patients (66.7%) reporting pain intensity greater than 3 points. In contrast, no pain syndrome was reported in group R.

The quality of life, assessed using the PAC-QOL scale, showed a significant decline in group O compared to the reference group across all parameters. Physical discomfort in group O worsened by 2.72 times (3.24 ± 0.44 vs. 1.19 ± 0.29); psychosocial discomfort by 2.19 times (1.84 ± 0.58 vs. 0.84 ± 0.18); anxiety by 2.66 times (2.05 ± 0.24 vs. 0.77 ± 0.24); satisfaction by 2.88 times (2.48 ± 0.59 vs. 0.86 ± 0.28); and the PAC-QOL score by 2.57 times (2.24 ± 0.25 vs. 0.87 ± 0.12), with $p < 0.05$ for all comparisons (Table).

Table. Values of PAC-QOL scores

PAC-QOL scales	Group O	Group R
Physical discomfort	3.24 ± 0.44 (2.00–3.75)	$1.19 \pm 0.29^*$ (0.25–1.75)
Psychosocial discomfort	1.84 ± 0.58 (1.13–2.88)	$0.84 \pm 0.18^*$ (0.50–1.38)
Worries and concerns	2.05 ± 0.24 (1.45–2.27)	$0.77 \pm 0.24^*$ (0.36–1.45)
Satisfaction and treatment	2.48 ± 0.59 (1.0–3.4)	$0.86 \pm 0.28^*$ (0.20–1.60)
PAC-QOL	2.24 ± 0.25 (1.86–2.71)	$0.87 \pm 0.12^*$ (0.61–1.18)

* $p < 0.05$.

According to the results, the clinical phenotype of patients with the Cajal subtype of chronic slow-transit constipation is characterized by an early disease onset (mean age at onset 8.67 ± 5.08 years) and a prolonged disease course (25.2 ± 11.2 years). Women predominated in this group (95.2%), with a mean age at the time of surgery of 33.9 ± 8.7 years. Typical features include infrequent bowel movements (mean interval between defecations 12.2 ± 4.3 days) and hard stool consistency (type 1 in 71.4% and type 2 in 28.6% according to the Wexner scale), with manual assistance required in 95.2% of cases.

A positive family history of the disease in first-degree relatives was registered in 50.5% of patients. Abdominal pain syndrome was present in 66.7% patients, with pain intensity exceeding 3 points on the VAS (mean value 2.8 ± 1.3).

These findings confirm the presence of severe clinical and functional disorders in patients with the Cajal subtype, identifying them as potential candidates for surgical treatment.

Discussion

Constipation remains a significant challenge in modern medicine, with substantial healthcare expenses associated with ineffective conservative treatments, leading to reduced patients' quality of life. Current data indicate that CSTC affects 2–4% of the general population. It is frequently resistant to conservative treatment, resulting in a high healthcare and social burden [3].

In recent literature, the Cajal subtype of CSTC has been identified in 19.6% of patients who underwent surgery [13], aligning with previous reports of ICC deficiency in patients with CSTC [4, 10, 18]. ICCs are intestinal «pacemaker» cells, and their reduction leads to colonic hypomotility, supporting the classification of the Cajal subtype as a morphologically distinct form of STC [2, 6, 9, 10].

Despite a variety of medications and dietary recommendations, CSTC associated with ICC deficiency is mostly unresponsive to standard treatment. Prospective reviews indicate that medical therapy provides only temporary relief, and radical interventions are necessary in refractory forms of the disease [18]. In such cases, subtotal or total colectomy with ileorectal anastomosis is recognized as the most effective treatment for refractory CSTC. Retrospective studies report that 81–93% of patients experience significant improvements in bowel movement frequency, overall functional status, and sustained quality of life post-colectomy [4, 7, 8, 11, 17].

Our study aimed to provide a detailed comparison of clinical and anamnestic characteristics, as well as

quality of life (PAC-QOL) measures, in patients with the Cajal subtype of CSTC compared to the reference group. Thus, the typical clinical picture of patients with the Cajal subtype of chronic slow-transit constipation is that of a woman approximately 34 years old, with disease symptoms beginning in childhood (mean age at onset: 8.7 years) and a disease duration exceeding 25 years. Half of these patients (50.5%) have a positive family history of constipation in first-degree relatives. The average defecation frequency is once every 12 days, with hard stool consistency (type 1–2 on the Wexner scale). A need for manual assistance is reported in 95.2% of cases. Additionally, 66.7% of patients experience abdominal pain, and there is a significant reduction in quality of life across all PAC-QOL domains.

This study included only patients after colectomy due to a refractory course of the disease. Consequently, the findings do not represent the full spectrum of clinical variability of the Cajal subtype of CSTC, but rather focus on the most severe cases requiring surgical intervention. Further research is necessary to include patients with milder forms who respond to conservative therapy, in order to establish clearer diagnostic criteria for this phenotype and potentially predict the disease course.

The limitations of this study include a sample comprised solely of surgical cases and the absence of preoperative functional assessments of colonic motility.

Future research should focus also on patients with early-stage Cajal-type CSTC, compare the effectiveness of various therapeutic strategies according to morphological subtypes, and developing stratification algorithms for surgical decision according to clinical, anamnestic, and morphological data.

Conclusions

The clinical phenotype of patients with the Cajal subtype who required surgical treatment was characterized by early disease onset at a young age (8.67 ± 5.08 years). These patients exhibited a high mean disease duration at presentation (25.24 ± 11.18 years; range 3–51), with a genetic predisposition evidenced by a positive family history in first-degree relatives in 50.5% of cases. They also experienced prolonged intervals between bowel movements (mean 12.2 ± 4.3 days) and lack of response to conservative therapy (100% refractory cases). Stool types 1 and 2 on the Wexner scale were observed in 71.4% and 28.6% of patients, respectively. Most patients required manual assistance during defecation (95.2%) and reported pronounced pain syndrome (VAS 2.8 ± 1.3) and a significant worsening of the overall PAC-QOL score (by 2.57 times).

DECLARATION OF INTERESTS

The authors declare that they have no conflicts of interest.

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AUTHORS CONTRIBUTIONS

Conception and design — I. M. Leshchyshyn, L. Y. Markulan; acquisition, analysis and interpretation of data — I. M. Leshchyshyn, O. I. Okhotska, P. L. Byk; statistical analysis — L. Y. Markulan; drafting the article — I. M. Leshchyshyn; critical revision of the article — I. M. Leshchyshyn, O. I. Okhotska.

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Клініко-анамнестичні характеристики та якість життя пацієнтів із кахальним підтипом хронічного повільно-транзитного запору

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Кажальний підтип хронічного повільно-транзитного запору (ХПТЗ), асоційований із дефіцитом клітин Кахалія, вважається найбільш резистентним до консервативної терапії. Його діагностика потребує гістологічного аналізу всіх шарів кишкової стінки, що пов'язано з інвазивністю та ризиком ускладнень. Тому клінічний фенотип цього підтипу недостатньо вивчений.

Мета — оцінити клініко-анамнестичні особливості та якість життя пацієнтів із кахальним підтипом хронічного повільно-транзитного запору після колектомії.

Матеріали та методи. За останні 12 років кахальний гістологічний підтип ХПТЗ був верифікований у 21 пацієнта після колектомії (група О). Групу порівняння утворено із 70 пацієнтів аналогічного віку та статі без ознак ХПТЗ (група R). Групи суттєво не відрізнялися за статтю, середнім віком та індексом маси тіла. У всіх пацієнтів були проаналізовані клініко-анамнестичні дані та якість життя за шкалою PAC-QoL.

Результати. В обох групах переважали жінки: 20 (95,2%) у групі О та 65 (92,9%) у групі R. Середній вік у групі О становив ($33,9 \pm 8,7$) року, у групі R – 41,5 року. Клінічний фенотип пацієнтів із кахальним підтипом, які потребували хірургічного лікування, характеризувався початком захворювання в молодому віці ($(8,67 \pm 5,08)$ року), тривалим перебігом до встановлення діагнозу (від 3 до 51 року, у середньому – $(25,24 \pm 11,18)$ року), генетичною схильністю (сімейний анамнез у родичів першого ступеня споріднення в 50,5% випадків), значними інтервалами між дефекаціями (у середньому $(12,2 \pm 4,3)$ доби), відсутністю відповіді на консервативну терапію, типом калу 1 та 2 за шкалою Wexner у 71,4 та 28,6% пацієнтів відповідно, необхідністю ручної допомоги під час дефекації (95,2%) та виразним больовим синдромом (за візуальною аналоговою шкалою – $2,8 \pm 1,3$). Якість життя за шкалою PAC-QoL була статистично значущо нижчою в групі О порівняно з групою R за всіма показниками: фізичний дискомфорт – у 2,72 разу ($3,24 \pm 0,44$ та $1,19 \pm 0,29$), психосоціальний дискомфорт – у 2,19 разу ($1,84 \pm 0,58$ і $0,84 \pm 0,18$), тривожність – у 2,66 разу ($2,05 \pm 0,24$ та $0,77 \pm 0,24$), задоволеність – у 2,88 разу ($2,48 \pm 0,59$ і $0,86 \pm 0,28$), загальний бал за PAC-QoL – у 2,57 разу ($2,24 \pm 0,25$ та $0,87 \pm 0,12$). Усі відмінності були статистично значущими ($p < 0,05$).

Висновки. Отримані результати підтверджують наявність тяжких клінічних і функціональних порушень у пацієнтів із кахальним підтипом ХПТЗ, що дає підстави розглядати їх як потенційних кандидатів на хірургічне лікування.

Ключові слова: хронічний повільно-транзитний запор, кахальний підтип, якість життя, шкала PAC-QoL.

FOR CITATION

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