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CHANGES IN THYROID HORMONES IN PATIENTS WITH CHRONIC ACALCULOUS CHOLECYSTITIS IN THE PRACTICE OF A FAMILY DOCTOR

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Abstract. Among biliary pathology, chronic acalculous cholecystitis (CAC) occupies one of the central places. The important role of the hormonal system in the regulation of the functioning of the biliary tract has been known for a long time, but the specific mechanisms of these influences remained unclear. Based on the results of a comprehensive clinical, laboratory, biochemical and instrumental examination, all patients with chronic acalculous cholecystitis were divided into three groups depending on the variant of impairment of the motor-kinetic function of the gallbladder. The first group consisted of patients with CAC and hypertensive-hyperkinetic gallbladder dyskinesia (group I) – 17 people; the second – patients with CAC with mixed hypotonic-hyperkinetic gallbladder dyskinesia (group II) – 19 people; the third – patients with CAC and hypotonic-hypokinetic dyskinesia of gallbladder (III group) – 29 people. The level of free FT_3, FT_4, and thyroid-stimulating hormone (TSH) was determined by the immunofluorescence method using BREAHMS test systems (Henning Berlin GMBH). The disproportion between the thyroid hormones and the quantitative predominance of the inactive form made it possible to identify the relative hypothyroid syndrome in group I patients. The disproportion between the biologically inactive and active forms of thyroid hormones with a quantitative predominance of the inactive form made it possible to judge the presence of a relative hypothyroid syndrome in group II patients. In group III patients, a significantly increased TSH level was revealed, which was a response of the hypothalamic-pituitary system to a decrease in the level of FT_3.

KEY WORDS: chronic acalculous cholecystitis, thyroid gland, hormones

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INTRODUCTION

In everyday practice, doctors of different specialties have to deal with diseases of the biliary tract: gastroenterologists, therapists, surgeons, emergency and emergency doctors. Among biliary pathology, chronic acalculous cholecystitis (CAC) occupies one of the central places. The most important task of the supervision of patients with chronic acalculous cholecystitis is to prevent the transformation of the process into gallstone disease. Decreased contractility of the gallbladder plays a critical role in the formation of gallstones [1]. Impaired gallbladder motility potentiates another important factor in cholelithiasis – bile cholesterol oversaturation [2]. Another important event associated with impaired gallbladder motility is the accumulation of lipids in the gallbladder wall [3]. The problem of lipid balance regulation is central to solving the clinical problem of preventing the progression of chronic acalculous cholecystitis.

The effect of thyroid hormones on lipid metabolism has been a topic of fundamental research for many years. Thyroid hormones help maintain the basal serum cholesterol levels needed to meet the body's normal needs for cell

synthesis and renewal. Thyroid hormones regulate serum cholesterol levels by stimulating cholesterol biosynthesis, export (primarily in the form of VLDL and LDL), reverse transport from peripheral tissues, liver reuptake through LDL (LDL) receptors and conversion to bile acids in the liver [4]. Thyroid hormones regulate lipid metabolism in the liver in a cell-autonomous manner, induce the expression of genes encoding proteins involved in liver lipogenesis. The possibility of using analogs and mimetics of thyroid hormones as therapeutic agents for the treatment of lipid-associated liver diseases is being studied [5]. The effect of thyroid hormones on the formation of gallstones was studied in vivo using an animal model: hypothyroidism causes the formation of cholesterol stones in the gallbladder, promoting cholesterol biosynthesis [6].

The interest in the role of the thyroid factor in the course of CAC is dictated by the great interest of clinicians in minor variants of hypothyroidism, which are found in the population much more often than clinical hypothyroidism. Subclinical thyroid dysfunction is defined as the change in serum thyroid-stimulating hormone (TSH) level relative to the reference interval at normal free thyroxine (FT_4) levels in asymptomatic patients [7]. The phenomenon is especially common in older women [8, 9].

The choice of parameters for monitoring thyroid balance indicators is also dictated by recent trends in thyroid ology. Measurement of TSH levels, although an indirect indicator of thyroid homeostasis, has become central to modern testing of thyroid function [10]. TSH has come to be regarded by the thyroid community as a simple and effective diagnostic parameter. The simplicity of measurement has been converted to simplicity of interpretation, ignoring the fact that TSH is both an indirect measure of thyroid hormone homeostasis and a control element. Thus, this concept of TSH dominance has led to the suppression of the complex relationship of the TSH response with various hormonal processes [11].

While recognizing the strategic benefits of TSH measurement, such as ease of use, suitability for first-line screening, detection of minor functional abnormalities, and association with various health outcomes, including mortality, there are significant risks of misrepresenting its complex physiological importance.

This is supported by the ongoing discussion around the TSH reference limits, especially its upper limit, which determines subclinical hypothyroidism [12]. TSH values are personalized indicators showing a high degree of individuality. The change in TSH concentration can be either simply adaptive to restore true euthyroidism, or a failed attempt to maintain the euthyroid state [13]. The pulsating nature of TSH secretion increases individual variations in TSH levels, which are significantly higher than the degree of individual fluctuations in FT_4 blood concentrations [14]. The same TSH value may be “normal” for one person, but pathological for another. This also applies to patients with subclinical dysfunction, in which the relationship between FT_4 and TSH shows both elements of normality and abnormalities [15].

OBJECTIVE

Knowledge of the mechanisms involved in the regulation of thyroid hormone balance has expanded significantly in recent years. The basic system is much more complex than previously thought, which dictates the need to revise old simplified concepts and promotes new multifactorial control concepts with feedback between the thyroid gland and the pituitary gland [16–18]. In the new integrative concept, TSH becomes a context-dependent conditional variable, and is neither an accurate marker of euthyroidism, nor an optimal criterion for fine-tuning thyroid control. A comprehensive interpretation of TSH, FT_4 and free triiodothyronite (FT_3) and their conditional equilibrium should be the basis for clinical decision-making [19].

The purpose of the work is the study of thyroid hormones in patients with CAC depending on dyskinetic disorders.

MATERIALS AND METHODS

Observation and examination of patients with CAC was carried out in the 26th polyclinic of Kharkov, which was the base of the department of general practice and family medicine of V. N. Karazin Kharkiv National University in the period from 2017 to 2019. A total of 65 patients with CAC were examined. The control group consisted of 12 healthy individuals. The surveyed group included

persons who did not have severe concomitant diseases.

The distribution of patients into clinical groups was carried out in accordance with the working classification of chronic non-calculous cholecystitis by V. A. Galkin (1986) and the classification of biliary dyskinesias by I. I. Degtyareva (1999).

Based on the results of a comprehensive clinical, laboratory, biochemical and instrumental examination (clinical blood test, C-reactive protein, total, conjugated and unconjugated bilirubin content in blood serum, gammaglutamyl transpeptidase, alkaline phosphatase, cholesterol, triglycerides, dynamic echosonocholecystoscopy, multiphase chromatographic duodenal intubation), all patients with chronic CAC were divided into three groups depending on the variant of impairment of the motor-kinetic function of the gallbladder. The first group consisted of patients with CAC and hypertensive-hyperkinetic gallbladder dyskinesia (group I) – 17 people; the second – patients with CAC with mixed hypotonic-hyperkinetic gallbladder dyskinesia (group II) – 19 people; the third – patients with CAC and hypotonic-hypokinetic dyskinesia of gallbladder (III group) – 29 people.

In the group of surveyed persons, women predominated, the ratio of men and women in the groups approached 1:5. Among the patients of group I, people aged 20 to 30 prevailed. In group II, the distribution of patients by age was almost uniform from 28 to 45 years. Patients in group III were predominantly 45–60 years old.

The hypertensive-hyperkinetic variant of gallbladder dyskinesia prevailed in patients with CAC disease up to 5 years. The mixed variant of gallbladder dyskinesia was equally encountered with the duration of the disease up to 5 years and from 5 to 10 years. The hypotonic-hypokinetic variant of gallbladder dyskinesia was more often detected in patients with the disease duration of more than 10 years.

In group I patients, pain was dominant (sudden colic in the right hypochondrium, intense, radiating to the right shoulder or scapula) and manifestations of neurovegetative dysfunction (emotional lability, sweating). The dominant dyspeptic phenomenon was recurrent moderately severe nausea.

Group II patients had mixed pain syndrome (a combination of background constant aching pains with episodes of colicky painful attacks). In comparison with patients of group I, the frequency of dyspeptic symptoms increased, among which the most common were bitterness in the mouth and poor appetite.

Patients of group III complained mainly of dull, constant aching pains without clear localization in the right hypochondrium. Dyspeptic symptoms were dominated by persistent bitterness in the mouth, poor appetite, severe flatulence, persistent constipation. Symptoms of asthenia (increased fatigue, decreased motivation and activity) were typical for this group, fever was often observed, with an increase in temperature to sub febrile numbers.

Abdominal pain syndrome was typical for all three studied groups of patients. The frequency of occurrence of dyspeptic syndrome in group II was higher than in group I, and in group III more than in group II. Neurovegetative syndrome was more typical for group I than for groups II and III. Asthenic syndrome was more common in group III than in groups I or II. The presence of exacerbation of CAC in patients at the time of examination was confirmed by the presence of segmental reflex symptoms. Pathological visceral skin reflexes were provoked by pressure with one finger on the corresponding organ-specific points of the skin. Irritative symptoms (Zakharyin, Volsky, Grekov-Ortner, Kera, Murphy, Obraztsov, Gausman) in various combinations were positive in all patients, which is a clinical marker during the period of exacerbation of patients with CAC. Segmental reflex symptoms of Mackenzie (pain when pressing on the Mackenzie pain point, located at the intersection of the outer edge of the right abdomen of the rectus abdominis muscle and the right costal arch); Boas (pain when pressing on Boas's pain point located along the right paravertebral line at the ThX-XI level), Aliev (antidromic irradiation of pain with pressure at the Mackenzie or Boas point) were positive in almost all patients of group III.

Signs of right-sided reactive syndrome were more often observed in group III of patients. Most often, pain was detected in the occipital point of Yonash, the cervical point of Mussi, in the parasolar pain points, in the region of the xiphoid process (Pekarsky's symptom) and below the angle of the right scapula (Karavanov's symptom).

To verify the diagnosis of chronic CAC in the examined patients, a complex of clinical, laboratory, biochemical and instrumental

research methods was used. All patients underwent ultrasound scanning of the thyroid gland and gallbladder. The contractile function of the gallbladder was clarified by performing dynamic echoscopy using an oral stimulator (two raw yolks). If there were sonographic signs of thyroid pathology, patients were excluded from the observation group.

The level of free FT_3, FT_4, and TSH was determined by the immunofluorescence method using BREAHMS test systems (Henning Berlin GMBH). The level of FT_3 and FT_4 and TSH in the blood serum of healthy individuals was (4,62 ± 0,28) and (14,45 ± 2,21) pmol/l, (3,31 ± 0,07) nmol/l, respectively.

The content of antibodies to thyroglobulin and antibodies to thyroperoxidase was determined using LUMItest-anti-TPO BREAHMS (Henning Berlin GMBH). In healthy individuals, the level of AT-TG and AT-TPO was (0,92 ± 0,05) and (0,57 ± 0,07) nmol/l, respectively. Determination of the level of AT-TG and AT-TPO was carried out in order to exclude autoimmune thyroiditis and other primary organic thyroid diseases.

Blood sampling to determine indicators of hormonal status was performed in the morning at 6–7 hours, after a night's sleep for 8–10 hours, on an empty stomach.

Statistical processing of the research results was carried out using the developed patient card, adapted for processing the results using the Microsoft Excel program. In the tables reflecting the results of our own research, for each indicator, the average value (M) and its error (m) are given. The results obtained were processed by the Student-Fisher statistical method using the standard package of functions «MS Excel» and «StatgraphWin».

Along with this, the thyroid status of patients with CAC was also studied. The results of the study confirming the presence of autoimmune thyroiditis or other thyroid diseases were negative (table 1). The level of antibodies to thyroglobulin and antibodies to thyroperoxidase did not exceed physiological concentrations. Ultrasound scanning of the thyroid gland revealed no abnormalities in the size and structure of the gland.

Table 1

Indicators of anti-thyroid autoantibodies (M ± m) in patients with CAC

Index	Control group (n = 12)	Groups of patients with CAC		
		I (n = 17)	II (n = 19)	III (n = 29)
AT-TG, nmol/l	0,92 ± 0,05	0,87 ± 0,06	0,74 ± 0,09	0,85 ± 0,07
AT-TPO, nmol/l	0,57 ± 0,07	0,60 ± 0,08	0,52 ± 0,11	0,64 ± 0,10

For a more in-depth study of the nature of hormonal relationships, some relative indicators were analyzed, representing the ratio of integer values of the studied hormones.

To investigate the violation of the relationship between the main thyroid hormones, the FT_4 / FT_3 index was used.

RESULTS

Changes in hormonal levels in patients of group I were characterized by a tendency towards a decrease in the level of FT_3 against the background of a trend towards an increase in the concentration of FT_4. The serum TSH level did not change. Along with this, the FT_4/FT_3 index significantly increased, which indicated a change in the ratio between the biologically active form of FT_3 and its inactive precursor FT_4 (table 2).

Table 2

Indicators of hormonal balance (M ± m) in patients of group I

Index	Control group (n = 12)	Patients I group (n = 17)	p
FT_3, pmol/l	4,62 ± 0,28	4,33 ± 0,11	p = 0,96
FT_4, pmol/l	14,45 ± 2,21	17,46 ± 0,29	p = 0,18
FT_4/FT_3	3,21 ± 0,07	4,07 ± 0,09	< 0,01
TSH, nmol/l	3,31 ± 0,44	3,75 ± 0,39	

The nature of the relationship between FT_4 and FT_3 changed. If healthy donors showed a weak direct correlation between FT_4 and FT_3: ($r = +0,18 \pm 0,04$; $p < 0,05$), then in group I patients the type of relationship between FT_4 and FT_3 changed – a weak negative relationship appeared ($r = -0,22 \pm 0,03$; $p < 0,05$).

Group II patients showed a tendency to decrease in the level of FT_3. The concentration of FT_4 in the blood serum tended to increase (table 3). The serum TSH content remained unchanged. However, the FT_4 / FT_3 index was significantly increased, which was a manifestation of an imbalance in the thyroid hormone system.

In group II patients, there was a weak negative relationship ($r = -0,31 \pm 0.03$; $p < 0,05$) between FT_4 and FT_3.

Table 3

Indicators of hormonal balance (M ± m) in patients of group II

Index	Control group (n = 12)	Patients with CAC, group II (n = 19)	p
FT_3, pmol/l	4,62 ± 0,28	4,25 ± 0,18	P = 0,66
FT_4, pmol/l	14,45 ± 2,21	17,94 ± 0,32	P = 0,12
FT_4/FT_3	3,21 ± 0,07	4,21 ± 0,13	< 0,01
TSH, nmol/l	3,31 ± 0,44	4,23 ± 0,41	

Patients in group III showed a significant decrease in the level of FT_3, while in patients in groups I and II, only a tendency towards a decrease in this indicator was observed. The concentration of FT_4 in the blood serum tended to increase (tab. 4). There were no significant differences between the content of FT_4 in the blood serum of patients with CAC with various variants of gallbladder dyskinesias. An increase in the FT_4 / FT_3 index was significant in group III patients. The value of the index FT_4 / FT_3 in them was significantly higher than in patients of group I (respectively $5,27 \pm 0,11$ и $4,07 \pm 0,09$, $p < 0,05$).

Table 4

Indicators of hormonal balance (M ± m) in patients of group III

Index	Control group (n = 12)	Patients with CAC, group III (n = 29)	p
FT_3, pmol/l	4,62 ± 0,28	3,65 ± 0,12	< 0,05
FT_4, pmol/l	14,45 ± 2,21	18,89 ± 0,61	p = 0,06
FT_4/FT_3	3,21 ± 0,07	5,27 ± 0,11	< 0,05
TSH, nmol/l	3,31 ± 0,44	5,48 ± 0,31	< 0,05

DISCUSSION

Since the main marker of thyroid hormone-forming activity is the level of FT_4, it can be considered that the cause of thyroid imbalance in patients of group I was not thyroid lesion, but a violation of the peripheral metabolism of FT_4 – a slowdown in the conversion of FT_4 to FT_3.

Such minimal changes in the balance of thyroid hormones are described in the literature as T_3-low-syndrome. This phenomenon in patients with CAC is of a non-thyrogenic nature, since there were no objective and subjective signs of thyroid lesion. The relative deficit of FT_3, revealed only when analyzing the indicator FT_4/FT_3, was most likely a manifestation of the adaptive response of the neuroimmunohormonal system of patients with CAC, aimed at reducing the severity of catabolic processes in conditions of exacerbation of the inflammatory process.

Thyroid status in mixed variant of gallbladder dyskinesia was characterized by the presence of minimal changes – a relative decrease in the level of FT_3 against the background of a relative increase in the level of FT_4. The imbalance of thyroid hormones with a relative predominance of the biologically inactive form of FT_4 can be regarded as a variant of T_3-low-syndrome. The cause of the

thyroid imbalance in group II patients, most likely, was not thyroid gland damage, but a violation of the peripheral metabolism of FT_4 – a slowdown in the conversion of FT_4 to FT_3.

Consequently, in patients of group III, more significant changes in the balance of thyroid hormones were observed. The deficiency of the biologically active form of FT_3 acquires the features of not a relative, but an absolute phenomenon in patients of group III. The change in the balance of hormones of the pituitary-thyroid system in group III patients consisted in the overproduction of TSH, a relative deficit of FT_3 against the background of a relative excess of FT_4.

The analysis of the role of the age factor caused certain difficulties. Loss of the contractile function of the gallbladder occurs as a result of prolonged progression of the pathological process in the gallbladder with a combination of several unfavorable factors, which include aging (the age of representatives of group III is significantly greater than in other groups). The groups could not be randomized according to age – in the real clinical practice of this institution, it was simply not possible to identify patients with this type of motor-evacuation disorders of gallbladder of a different age.

The problem of the reliability of the classical TSH indicator as a criterion for diagnosing thyroid insufficiency in the aging population is being discussed quite actively, there are many reports of an increase in the level of circulating TSH in older people [20]. The impressive Baltimore Long-Term Aging Study (BLSA), a long-term study of 1,483 participants who underwent thyroid function tests between 2003 and 2015.

The mean TSH value progressively increased with age from 2,4 mIU / L in persons under 60 years of age to 2,6 mIU/L in persons aged 60–69 years, 2,7 mIU/L in persons aged 70–79 years and 3,2 mIU/L in persons > 79 years old. The increase in the mean TSH value is not linear, but mainly refers to the oldest age group in persons over 79 years old [21]. Patient group III was much younger, up to 60 years old, so the factor of age-related increase in TSH level cannot be considered decisive. Non-thyroid factors are often considered as possible causes of increased TSH levels. TSH is proposed to be considered as an early predictor of stress, more sensitive than levels of cortisol, glucose or norepinephrine [22].

CONCLUSIONS

1. The disproportion between the thyroid hormones and the quantitative predominance of the inactive form made it possible to identify the relative hypothyroid syndrome in group I patients.

At the same time, the quantitative relationships between hormones change, which can be used as additional diagnostic criteria.

2. The disproportion between the biologically inactive and active forms of thyroid hormones with a quantitative predominance of the inactive form made it possible to judge the presence of a relative hypothyroid syndrome in group II patients. Thus, the general anabolic-catabolic potential of the organism is somewhat leveled.

3. Patients of group III showed a significantly increased level of TSH, which was a response of the hypothalamic-pituitary system to a decrease in the level of FT_3. Thus, the hypothalamic-pituitary system reacts to thyroid imbalance as hypothyroid syndrome.

The results of the studies carried out in patients with CAC have revealed the peculiarities of changes in the hormonal status. Various changes in the hormonal status of patients were observed depending on the type of dyskinetic disorders in the gallbladder. There was a syndrome of hormonal dysfunction, which characterized the tension of the body's adaptive systems.

PROSPECTS FOR FUTURE STUDIES. AUTHOR CONTRIBUTIONS

Further study of hormonal characteristics in this category of patients and the development of rational treatment regimens are promising.

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ЗМІНИ ГОРМОНІВ ЩИТОПОДІБНОЇ ЗАЛОЗИ У ХВОРИХ НА ХРОНІЧНИЙ НЕКАЛЬКУЛЬОЗНИЙ ХОЛЕЦИСТИТ В ПРАКТИЦІ СІМЕЙНОГО ЛІКАРЯ

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Резюме. Серед патології жовчовивідних шляхів одне з центральних місць займає хронічний некалькульозний холецистит (ХНХ). Важлива роль гормональної системи в регуляції функціонування жовчовивідних шляхів відома давно, але конкретні механізми цих впливів залишалися неясними. За результатами комплексного клінічного, лабораторного, біохімічного та інструментального обстеження всі пацієнти з хронічним некалькульозним холециститом були розділені на три групи в залежності від варіанту порушення моторно-кінетичної функції жовчного міхура. До першої групи увійшли пацієнти з ХНХ та гіпертонічно-гіперкінетичною дискінезією жовчного міхура (I група) – 17 осіб; друга – пацієнти з ХНХ зі змішаною гіпотонічно-гіперкинетичною дискінезією жовчного міхура (II група) – 19 осіб; третя - пацієнти з ХНХ та гіпотонічно-гіпокінетичною дискінезією жовчного міхура (III група) – 29 осіб. Рівень вільного T_3, T_4 і тиреотропного гормону (ТТГ) визначали імунофлуоресцентний методом з використанням тест-систем BREAHMS (Henning Berlin GMBH). Диспропорція гормонів щитовидної залози і кількісне переважання неактивної форми дозволили виявити відносний гіпотиреоїдних синдром у пацієнтів I групи. Диспропорція між біологічно неактивними і активними формами тиреоїдних гормонів з кількісним переважанням неактивної форми дозволила судити про наявність відносного гіпотиреоїдного синдрому у пацієнтів II групи. У пацієнтів III групи виявлено достовірне підвищення рівня ТТГ, що є відповіддю гіпоталамо-гіпофізарної системи на зниження рівня FT_3.

КЛЮЧОВІ СЛОВА: хронічний некалькульозний холецистит, щитоподібна залоза, гормони

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ИЗМЕНЕНИЕ ГОРОМОНОВ ЩИТОВИДНОЙ ЖЕЛЕЗЫ У БОЛЬНЫХ ХРОНИЧЕСКИМ НЕКАЛЬКУЛЕЗНЫМ ХОЛЕЦИСТИТОМ В ПРАКТИКЕ СЕМЕЙНОГО ВРАЧА

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Резюме. Среди патологии желчевыводящих путей одно из центральных мест занимает хронический некалькулезный холецистит (ХНХ). Важная роль гормональной системы в регуляции функционирования желчевыводящих путей известна давно, но конкретные механизмы этих влияний оставались неясными. По результатам комплексного клинического, лабораторного, биохимического и инструментального обследования все пациенты с хроническим некалькулезным холециститом были разделены на три группы в зависимости от варианта нарушения моторно-кинетической функции желчного пузыря. В первую группу вошли пациенты с ХНХ и гипертонически-гиперкинетической дискинезией желчного пузыря (I группа) – 17 человек; вторая – пациенты с ХНХ со смешанной

гипотонико-гиперкинетической дискинезией желчного пузыря (II группа) – 19 человек; третья – пациенты с ХНХ и гипотоно-гипокинетической дискинезией желчного пузыря (III группа) – 29 человек. Уровень свободного T_3, T_4 и тиреотропного гормона (ТТГ) определяли иммунофлуоресцентным методом с использованием тест-систем BREAHMS (Henning Berlin GMBH). Диспропорция гормонов щитовидной железы и количественное преобладание неактивной формы позволили выявить относительный гипотиреоидный синдром у пациентов I группы. Диспропорция между биологически неактивными и активными формами тиреоидных гормонов с количественным преобладанием неактивной формы позволила судить о наличии относительного гипотиреоидного синдрома у пациентов II группы. У пациентов III группы выявлено достоверное повышение уровня ТТГ, что является ответом гипоталамо-гипофизарной системы на снижение уровня FT_3.

КЛЮЧЕВЫЕ СЛОВА: хронический некалькулезный холецистит, щитовидная железа, гормоны

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