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Parietal and occipital hair loss patterns in initial stages of androgenetic alopecia in men

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Background. The initial stages of androgenetic alopecia in men are characterized by a variety of clinical manifestations in the parietal or occipital scalp regions. However, the differences in the pathogenesis of hair loss patterns are not well understood; no selective treatment has been developed.
Objectives. To assess the trichological characteristics of patients with initial stages of androgenetic alopecia, identify the genetic and non-genetic factors being responsible for hair loss in different scalp regions, and assess patients' response to conservative therapy.
Materials and Methods. Trichograms were photodocumented using an AramoSG microcamera (Republic of Korea). The genetic factor was analyzed by minisequencing of single nucleotide polymorphisms rs929626, rs5919324, rs1998076, rs12565727, and rs756853. The study of non-genetic factors involved assessment of the hormonal status (total and free testosterone, dihydrotestosterone, 17OH-progesterone, dehydroepiandrostenone, and SHBG) and blood contents of trace elements (Mg, Ca, Zn, Cu, Se, Fe) and vitamins (B12, D, E, folic acid). Conservative treatment consisted of topical application of 5% minoxidil (twice daily, 4 months) and personalized correction of micronutrient deficiencies.
Results. The study involved 47 males with initial stages of androgenetic alopecia. Their trichological examination showed two patterns consisting in a predominant decrease in hair density and diameter in the parietal and occipital scalp regions, which were the criteria for patient allocation into subgroups. Intergroup comparison revealed similar genetic risk, while hormonal parameters (increased dihydrotestosterone levels and decreased free testosterone) characterized the subgroup with the parietal hair loss pattern. Multiple deficiency of Zn, Cu, Se and vitamins B12, D, and folic acid was also detected in all the patients. Subsequent conservative treatment had a positive effect in patients with the parietal hair loss pattern, while no significant response was observed in patients with the occipital pattern.
Conclusions. The study develops ideas about differences between the androgen-dependent parietal and androgen-independent occipital hair loss patterns in the initial stages of androgenetic alopecia, requiring different approaches to their conservative therapy.

Keywords: **androgenetic alopecia, hair loss patterns, pathogenesis, conservative therapy**

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Париетальный и окципитальный паттерны утраты волос при ранних стадиях андрогенной алопеции у мужчин

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Обоснование. Ранние стадии андрогенной алопеции характеризуются разнообразием вариантов течения, неравномерно затрагивающих париетальную или окципитальную области кожи головы. Однако различия в патогенезе данных состояний изучены недостаточно, а протоколы их терапии не обоснованы.
Цель исследования. Анализ трихологических характеристик пациентов с ранними стадиями андрогенной алопеции с идентификацией генетических и негенетических факторов, определяющих утрату волос в париетальной и окципитальной зонах скальпа, а также выраженность отклика на консервативную терапию данного заболевания.
Методы. Характеристики трихограмм проанализированы с использованием микрокамеры Aramo SG (Республика Корея). Роль генетического фактора оценена на основе однонуклеотидных полиморфизмов rs929626, rs5919324, rs1998076, rs12565727, rs756853. Исследование негенетических факторов включало показатели гормонального фона (общий и свободный тестостерон, дигидротестостерон, 17OH-прогестерон, дегидроэпиандростенон, ГСПГ), а также содержание в плазме крови микроэлементов (Mg, Ca, Zn, Cu, Se, Fe) и витаминов (B12, D, E, фолиевой кислоты). Использованный вариант консервативной терапии предусматривал местное применение 5% раствора миноксидила (2 раза в день в течение 4 месяцев), дополняемое персонализированной коррекцией выявленных микронутриентных дефицитов.
Результаты. В исследование включены 47 пациентов с ранними стадиями андрогенной алопеции. Их трихологическое обследование показало два варианта течения данного заболевания, заключающиеся в неравномерном уменьшении плотности и диаметра волос в париетальной и окципитальной зонах скальпа, что явилось обоснованием для формирования соответствующих подгрупп. Сравнительный анализ в подгруппах показал сходный уровень генетического риска, в то время как параметры гормонального фона (повышенный уровень дигидротестостерона при снижении свободного тестостерона) статистически значимо выделяли пациентов с париетальным паттерном утраты волос. На этом фоне множественные дефициты Zn, Cu, Se и витаминов B12, D, фолиевой кислоты были характерны для всех пациентов с ранними стадиями андрогенной алопеции. Последующая консервативная терапия позволила достичь выраженного клинического эффекта у пациентов с париетальным паттерном утраты волос, в то время как пациенты с окципитальным паттерном не демонстрировали значимого улучшения параметров трихограмм.
Заключение. Результаты проведенного исследования формируют представления об андроген-зависимом париетальном и андроген-независимом окципитальном паттернах утраты волос при ранних стадиях андрогенной алопеции, требующих разных терапевтических подходов.

Ключевые слова: **андрогенная алопеция; паттерны утраты волос; патогенез; консервативная терапия**
Конфликт интересов: авторы данной статьи подтвердили отсутствие конфликта интересов, о котором необходимо сообщить.
Источник финансирования: рукопись подготовлена и опубликована за счет финансирования по месту работы авторов.
Выражение признательности: авторы выражают искреннюю благодарность пациентам и здоровым добровольцам, принявшим участие в проведении исследования.
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Background

Androgenetic alopecia (ICD-10 code L64) is the most common type of pathological hair loss [1], whereas alopecia areata, cicatricial alopecia, and other types of alopecia are much rarer in modern clinical practice. This disease is characterized by well-discernible stages of progressive hair loss, which is represented in most of the proposed classification systems, the Hamilton–Norwood scale being the most popular one [2]. Early stages (I–IV) of androgenetic alopecia are characterized by a broad variety of hair loss patterns in different scalp regions, which should be regarded as specific types of the disease preferentially affecting the parietal or occipital regions [3]. The current position on importance of biophysical and physiological parameters in these scalp regions, which are considered to be androgen-dependent and androgen-independent, are another argument in favor of analyzing these patterns individually [4].

The contemporary views on the mechanisms of the onset and development of androgenetic alopecia indicate that this disease has a multifactorial pathogenesis, which is determined by combined action of a number of genetic and non-genetic factors [5]. Thus, the modern DNA analysis techniques have made it possible to identify genetic polymorphisms associated with the risk of developing androgenetic alopecia [6] and predominantly related to loci encoding cellular development and cytodifferentiation. In turn, elevated levels of male sex hormones (androgens), and dihydrotestosterone (whose effect consists in reduction of the phase of active hair growth (anagen), lengthening of the regression phase (telogen), miniaturization and fewer total number of hair follicles) in particular, have conventionally been regarded as the key non-genetic factor responsible for the development of androgenetic alopecia [7]. Individual vitamins and micronutrients whose deficiency presumably has a negative effect on the trophism of skin appendages have been identified as other non-genetic factors [8]. Integral consideration of these factors within a unified multi-parametric model has made it possible to elaborate a theoretically substantiated system for predicting the onset and development of androgenetic alopecia in men [9], whereas their role in identification of different hair loss patterns at early disease stages has remained beyond the scope of the conducted analysis.

Due to the progress in understanding the pathogenesis of androgenetic alopecia, there has been interest in developing conservative therapy modalities for this disease, which aim to restore the structure and function of hair follicles. A very extensive range of tools has currently been proposed for this purpose [10], including finasteride (an inhibitor of 5α-reductase catalyzing testosterone to dihydrotestosterone conversion), minoxidil (a vasodilator acting as an agonist of nitric oxide receptors and an adenosin-5'-triphosphate-sensitive potassium channel opener), as well as various nutraceuticals and folk remedies [11]. Meanwhile, the gold standard of therapy for early-stage androgenetic alopecia still needs to be elaborated; there are no Russian clinical guidelines for this problem, while the existing international guidelines do not involve information on restoration of hair growth in individual scalp regions.

Objective: To assess the pattern of hair loss in the parietal and occipital scalp regions in patients with early-stage androgenetic alopecia, analyze the key pathogenetic factors responsible for the preferential hair loss in the investigated scalp regions, and assessing the effectiveness of conservative treatment of this disease.

Methods

Study design

The study was conducted in compliance with the principles of evidence-based medicine. Case–control study was performed for the part where genetic and non-genetic factors responsible for different hair loss patterns were identified, while prospective cohort study design was used to analyze effectiveness of conservative therapy of early-stage androgenetic alopecia.

Eligibility criteria

Examination of patients in the study and control groups, as well as treatment in study subgroups, were conducted in compliance with the standards of primary medical care for patients with androgenetic alopecia (approved by the Order of the Ministry of Health of the Russian Federation dated March 25, 2013; registration number 27867).

The inclusion criteria for the study group were as follows: males with verified clinical diagnosis of androgenetic alopecia (ICD-10 code L64), hair loss corresponding to stages I–IV according to the Hamilton–Norwood scale. Other types of alopecia, as well as cases when hair loss was a complication of another disease, were the non-inclusion criteria. The criteria for including patients in the control group were normal parameters of scalp trichogram and no signs of alopecia in subject's parents or close relatives.

Study conduct

Clinical examination and analysis of the parameters of trichograms and phototrichograms were conducted at the Consultative and Diagnostic Department of the State Research Center for Dermatovenereology and Cosmetology of the Ministry of Health of the Russian Federation. The genetic markers of the risk of developing androgenetic alopecia were studied at the Department of Laboratory Diagnosis of Sexually Transmitted Infections and Dermatosis; the non-genetic markers were analyzed at the laboratory center of the same medical institution.

Study duration

Allocation of patients into the study and control groups was performed during the period between January 2017 and December 2018. Conservative treatment of patients in subgroups and instrumented assessment of its effectiveness was carried out during the period between July 2017 and June 2019.

Description of medical intervention

Quantitative characteristics of hair (separately in the parietal and occipital scalp regions) were assessed by analyzing trichograms and phototrichograms recorded using an Aramo SG (Aram HUVIS Co. Ltd., Republic of Korea) and processing the resulting images using the professional hair and scalp diagnostic software Trichoscience PRO v.1.4. The following parameters were assessed: hair density (HD) characterized by number of hairs per cm^2; hair diameter (D) expressed in μm; and the proportion of anagen and telogen hair expressed as a percentage with respect to the total number of pigmented hair shafts. Details of the method were described earlier [9].

During the same period, venous blood samples (5–10 mL) were collected from each study subject into Vacuette K3 tubes containing EDTA (Greiner Bio-One, Austria) and subsequently separated into the cellular and plasma fractions by centrifugation in an Allegra X-14 centrifuge (Beckman Coulter, USA) at 3000 g during 10 min.

The cellular fraction was used to isolate total DNA, which was analyzed by minisequencing to identify A/G single-nucleotide polymorphisms (SNPs) at rs5919324, rs1998076, rs929626, rs12565727, and rs756853 loci according to the procedure described previously [9].

Blood plasma was separated into aliquots; some of them were used to analyze the hormonal status (total and free testosterone, dihydrotestosterone, 17-OH-progesterone, dehydroepiandrostenone, and SHBG levels) by enzyme-linked immunosorbent assay (ELISA) using test kits (DRG Instruments GMbH, Germany) on a Multiscan Ascent microplate photometer (Thermo Scientific, USA).

The remaining aliquots were provided for measuring concentrations of trace elements and vitamins. The contents of Mg, Ca, Zn, Cu, Se, and Fe were analyzed by direct colorimetry on a KONELAB 20XTi biochemistry analyzer (Thermo Scientific, USA) or by atomic absorption spectrometry on the AA-7000 platform (Shimadzu, Japan). Concentrations of vitamins B12, D, E and folic acid were determined by ELISA, luminescence immunoassay, and high-performance liquid chromatography coupled with mass spectrometry on the EVOQ TQ MS platform (Bruker Daltonik GmbH, Germany).

Once examination had been completed, all the study group patients received basic conservative treatment with 5% minoxidil solution (applied topically, twice daily) during four months; personalized correction of the revealed micronutrient and vitamin deficiencies was also performed within the first two months. This correction included administration of one or more available dosage forms of magnesium orotate dihydrate (500 mg twice daily), zinc sulfate (124 mg twice daily), copper chelate (400 mg once daily), selenium (50 μg twice daily), iron (III)–hydroxide polymaltose complex (357 mg once daily), vitamin B12 (1 mg IM every other day N = 10), vitamin D3 (5000 IU once daily), vitamin E (400 mg once daily), and folic acid (5 mg once daily).

Study outcomes

Primary outcome: The effectiveness of conservative therapy of early-stage androgenetic alopecia was assessed according to the direct objective criterion: changes in quantitative characteristics of hair with calculated difference (Δ) of each analyzed parameter in each individual patient before and after completion of therapy course.

Subgroup analysis

Subgroups of patients with preferential hair loss in the parietal and occipital scalp regions were formed from the overall study group of patients with early-stage androgenetic alopecia based on comprehensive consideration of trichogram and phototrichogram data documented during initial examination. Association of each patient with a certain hair loss pattern was determined using the highest value of the respective score calculated by factor analysis (see below). During further subgroup analysis, patients were compared to the control group according to the genetic risk of developing androgenetic alopecia, hormonal characteristics, as well as the micronutrient and vitamin status. Subgroup analysis was also conducted when assessing the effectiveness of conservative treatment.

Ethical expertise

The study conduct was approved by the Local Ethics Committee of the State Research Center for Dermatovenereology and Cosmetology, Ministry of Health of the Russian Federation (Protocol No. 7 dated October 31, 2017) and was found to comply with the standards of Good Clinical Practice and evidence-based medicine.

Statistical analysis

Principles of sample size calculation:

Sample size calculation was not preliminarily calculated.

Statistical analysis methods:

The data were analyzed using the STATISTICA 13.0 software package (StatSoft Inc., USA). The threshold values $p < 0.05$, $p < 0.01$, and $p < 0.001$ were statistical criteria used to prove differences between groups and subgroups. Algorithms of multiple correlation and factor analysis were employed for analyzing trichogram parameters significant for identifying the parietal and occipital hair loss patterns.

Results

Study participants (subjects)

A total of 47 patients with early manifestations of androgenetic alopecia (ICD-10 code L64) corresponding to stages I–IV of the disease according to the Hamilton–Norwood scale were included in the study. Their baseline trichological examination provided a thorough quantitative description of hair in the parietal and occipital scalp regions; further statistical analysis of the resulting data gave an idea about the key relationships and factors characterizing the hair loss patterns in the scalp regions being compared.

The strongest inverse correlations were observed for the proportion of telogen (T) and anagen (A) hair in the parietal ($r = –1.00$; $p < 0.001$) and occipital ($r = –0.91$; $p < 0.001$) regions, which was supplemented by existence of statistically significant positive coefficients of correlation between the proportion of hair that were in the anagen ($r = 0.66$; $p < 0.001$) or telogen phases simultaneously in both scalp regions. The integral consideration of these parameters in accordance with the factor analysis algorithm demonstrated that the proportion of anagen and telogen hair played a crucial role in the development of androgenetic alopecia (factor F1 = 3.65; explained variance 45.6%), which was consistent with the views on the universal mechanisms of the pathogenesis of this disease consisting in shortening of the active growth phase and lengthening of the resting phase followed by hair loss [12].

On the other hand, the second (F2) and third (F3) most important factors revealed by multiparametric analysis of trichograms perfectly correlated with hair density (HD) and diameter (D) in individual scalp regions (Fig. 1*a*). Thus, the structure of factor F2 (value 1.47; explained variance 18.4%) was composed of the high factor loading of the variables hair diameter (0.827) and density (0.787) in the parietal region, which was typical of 27 out of 47 subjects in the analyzed sample. In turn, the remaining 20 patients were associated with factor F3 (value 1.22; explained variance 15.2%); its feature depended on the high factor loading for the variable hair diameter (0.804) in the occipital region, supplemented by a somewhat less significant value (0.554)

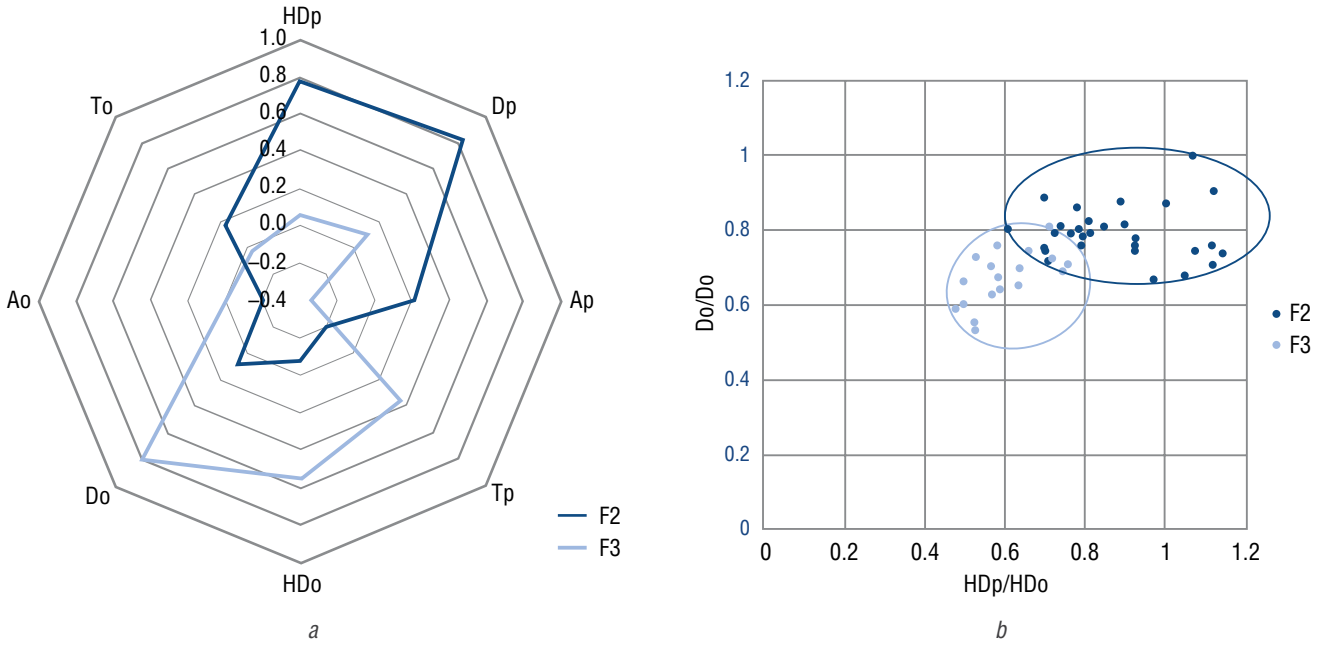

Fig. 1. Trichogram parameters characteristic of the parietal (F2) and occipital (F3) hair loss patterns in early-stage androgenetic alopecia in men; (*a*) the structure F2 and F3 factors including significance of trichogram parameters (from +1.0 to –1.0); (*b*) the distribution of hair diameter (D) and hair density (HD) ratios in the parietal and occipital zones in patients associated with F2 and F3 factors

Рис. 1. Параметры трихограмм, дифференцирующие париетальный (F2) и окципитальный (F3) паттерны утраты волос при ранних стадиях андрогенной алопеции: *a* — структура факторов F2 и F3 с определяющими их факторными нагрузками отдельных параметров трихограммы (от +1,0 до –1,0); *b* — распределение соотношений диаметра (D) и плотности волос (HD) в париетальной и окципитальной зонах у пациентов, ассоциированных с факторами F2 и F3

of factor loading for the variable hair density in the same scalp region.

Calculation of secondary variables proposed by Vecchio et al. [13; 14], which showed the relationship between hair diameter and density in the parietal and occipital regions in individual patients with their representation in the respective coordinate system (x = HDp/HDo; y = Dp/Do), proved that two alternative hair loss patterns detected in subgroups consisting of 27 and 20 patients do objectively exist (Fig. 1*b*).

Hence, the results obtained gave grounds for continuing the in-depth study of our sample aiming to identify genetic and non-genetic factors responsible for preferential hair loss in the parietal and occipital scalp areas at early stages of androgenetic alopecia in men.

Primary findings

Further analysis in subgroups consisting of 27 and 20 patients was supplemented by comparison with the control group consisting of 25 age- and sex-matched volunteers who had no objective signs of hair loss when the study was conducted.

Genetic risk factors were analyzed by studying five single nucleotide polymorphisms (SNPs): rs929626, rs5919324, rs1998076, rs12565727, and rs756853, whose role in the development of androgenetic alopecia has been previously proved [15]. For individual SNPs, statistically significant differences in frequencies were demonstrated for homozygous carriers of the high-risk GG alleles in the rs12565727, rs756853, and rs929626 loci (Table 1). Thus, in the rs12565727 locus residing in the *TARDBP* gene (encoding the DNA-binding protein, transcription suppressor TDP-43), no homozygous GG genotype was found in subgroup F2, which was important for ensuring its difference with the control group ($p < 0.05$); contrariwise, it was most frequently observed in subgroup F3 ($p < 0.001$). Another case of the homozygous GG genotype responsible for differences in subgroups F2 and F3 was related to the rs756853 locus in the *HDAC9* gene (encoding histone deacetylase 9): its frequency in patients with the occipital hair loss pattern was 2.5-fold higher than that in patients with the parietal hair loss pattern and 3.25-fold higher than that in the control group ($p < 0.01$). The third observation was the high frequency of the GG allele in the rs929626 locus in intron of the EBF1 gene (encoding early B-cell factor 1) that was typical of subgroups F2 and F3, which made these patients differ qualitatively from the control group in terms of this SNP. Therefore, these data suggested that significance of the genetic factor was somewhat higher in the subgroup of patients with the occipital hair loss pattern (F3) compared to the other subgroup having the parietal hair loss pattern (F2); however, calculation of the integral parameter in accordance with the previously elaborated algorithm [9] demonstrated that proportions of patients with a high genetic risk of developing alopecia were nearly equal in subgroups F2 (66%) and F3 (61%).

An analysis of the hormonal status of patients with androgenetic alopecia (Table 2) revealed oppositely directed changes in total testosterone and dihydrotestosterone levels in subgroup F2. Whereas plasma level of dihydrotestosterone in subgroup F2 subjects was elevated to 1132.2 ± 664 pg/mL vs 627.6 ± 192.8 pg/mL in the control group ($p < 0.001$), the total testosterone level was decreased: 19.9 ± 11.9 nmol/L vs 27.1 ± 13.9 nmol/L in the control group ($p < 0.05$). Therefore, this finding was consistent with the long-held views on the role of increased activity of 5α-reductase, which has conventionally been considered one of the mechanisms

Table 1. Expression of markers depending on the type of EPD during immunohistochemical examination
Таблица 1. Экспрессия маркеров в зависимости от типа ЭРП при иммуногистохимическом исследовании

Analyzed SNP and its position in the genome	Genotype	Control group (*n* = 25)	Subgroup F2 (*n* = 27)	Subgroup F3 (*n* = 20)
rs12565727, the *TARDBP* gene	AA	64	58	63
	AG	32	42	26
	GG	4	0*	11***
rs756853, the *HDAC9* gene	AA	36	31.5	33
	AG	56	58	41
	GG	8	10.5	26**
rs929626, the *EBF1* gene	AA	32	26	22
	AG	64	53	44
	GG	4	21***	33***
rs1998076, located between the *PAX1* and *FOXA2* genes	AA	24	15.8	14.9
	AG	40	52.6	44.4
	GG	36	31.6	40.7
rs5919324, located upstream of the androgen receptor gene	A	88	84.2	89
	G	12	15.8	11

The differences are significant: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
Различия достоверны: * $p < 0,05$; ** $p < 0,01$; *** $p < 0,001$.

Table 2. The blood levels of hormones, trace elements and vitamins in patients with early-stage androgenetic alopecia (F2 and F3 subgroups) vs the control group
Таблица 2. Содержание гормонов, микроэлементов и витаминов в плазме крови пациентов с ранними стадиями андрогенной алопеции (подгруппы F2 и F3) относительно контрольной группы

Parameters analyzed	Control group (*n* = 25)	Subgroup F2 (*n* = 27)	Subgroup F3 (*n* = 20)
Total testosterone (nmol/L)	27.1 ± 13.9	19.9 ± 11.9*	25.8 ± 16.5
Free testosterone (pg/mL)	20.0 ± 10.0	21.1 ± 12.6	17.2 ± 9.2
Dihydrotestosterone (pg/mL)	627.6 ± 192.8	1132.2 ± 664***	828.9 ± 551.6
17-OH-progesterone (ng/mL)	1.2 ± 0.5	1.4 ± 0.6	1.7 ± 0.9**
Androstenedione (ng/mL)	1.9 ± 0.8	2.3 ± 1.2	2.1 ± 1.6
SHBG (nmol/mL)	38.4 ± 20	31.7 ± 12.3	40.6 ± 21.5
Mg (mmol/L)	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.2***
Ca (mmol/L)	2.4 ± 0.1	2.4 ± 0.1	2.3 ± 0.1
Zn (μmol/L)	13.5 ± 2	11.6 ± 3.2*	11.3 ± 3.4*
Cu (μmol/L)	18.1 ± 2.7	12.2 ± 3.9***	12.7 ± 4.7***
Se (μg/L)	1.0 ± 0.1	0.8 ± 0.3**	0.7 ± 0.2***
Fe (μmol/L)	24.4 ± 4.9	21.0 ± 6.7*	24.0 ± 7.3
Vitamin B12 (pg/mL)	501.0 ± 273.1	366.7 ± 194.6*	331.7 ± 247.9*
Vitamin D (ng/mL)	47.2 ± 14.5	29.2 ± 12.2***	24.6 ± 13.4***
Vitamin E (μg/mL)	10.8 ± 3.9	6.8 ± 4*	8.8 ± 4.4
Folic acid (ng/mL)	10.8 ± 2.6	5.3 ± 3.0***	7.8 ± 4.9*

The differences are significant: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
Различия достоверны: * $p < 0,05$; ** $p < 0,01$; *** $p < 0,001$.

of developing androgenetic alopecia [16]; as a result, testosterone is actively converted to dihydrotestosterone that strongly binds to androgen receptor and triggers transcription of target genes when migrating to the nucleus of hair follicle cells. Meanwhile, these hormonal shifts were not observed in subgroup F3 subjects; the only finding was the elevated level of 17-OH-progesterone (1.7 ± 0.9 ng/mL vs 1.2 ± 0.5 ng/mL in the control group; $p < 0.01$), which is a precursor for cortisol and regulates the catabolic processes, blood pressure, and activity of the immune system through it. Nonetheless, our findings prove the canonical androgen-dependent mechanism of the development of androgenetic alopecia in the parietal scalp region, thus indicating that there are other reasons for occipital hair loss, which may be partially related to altered adrenal function and metabolic disorders caused by it.

The third group of parameters analyzed involved micronutrients: minerals and vitamins playing a crucial role in the normal hair follicle cycle [8]. The present study has proved it as it has been demonstrated that a number of parameters in subgroups F2 and F3 were statistically significantly changed with respect to the control group (Table 2). Synchronous decline in the levels of Zn, Cu, and Se minerals as well as vitamins B12, D, and folic acid was observed in all the patients with androgenetic alopecia; patients in subgroup F2 also had Fe and vitamin E deficiency, while patients in subgroup F3 had reduced Mg level. In turn, differences between the subgroups of patients with androgenetic alopecia preferentially characterized by parietal or occipital hair loss patterns were much less pronounced and referred to the parameters mentioned previously: profound folic acid deficiency in subgroup F2 and reduced Mg level in subgroup F3. In combination with the data obtained earlier [16] and demonstrating that hair density and diameter depend on the plasma level of some minerals and vitamins in patients with androgenetic alopecia, the results of this study broaden the views on the multifactorial nature of this disease and evaluate the prospects of personalized correction of micronutrient deficiencies as an additional tool for conservative therapy.

Secondary findings

Basic conservative therapy of early-stage androgenetic alopecia involved topical application of 5% minoxidil solution twice daily during four months in combination with two-month personalized correction of mineral and vitamin deficiencies detected at baseline examination. Objective assessment of the outcomes was based on comparative analysis of trichograms (calculating Δ) before and immediately after the full therapy course had been completed.

The analysis in subgroups F2 and F3 revealed significant differences in success of the therapy regimen used, as well as features of response to therapy in the parietal and occipital scalp regions (Table 3). The statistically significant progress in hair regeneration was observed in subgroup F2 (the oppositely directed changes in the proportion of anagen (Δ = 10.03%; $p < 0.01$) and telogen (Δ = –9.80%; $p < 0.01$) hair in the parietal region; increased hair density (Δ = 21.50 hairs per cm^2; $p < 0.05$) and diameter (Δ = 5.90 μm; $p < 0.001$) in this scalp region. Positive changes in the ratio between anagen (Δ = 6.09%; $p < 0.01$) and telogen (Δ = –5.04%; $p < 0.05$) hair in the occipital region was documented for the same subgroup; however, it was insufficient for to statistically significantly increase hair diameter and density. On the other hand, while the overall dynamics in trichograms were similar, no statistically significant changes in analyzed parameters were observed in subgroup F3, being indicative of insufficient response of patients preferentially having the occipital hair loss pattern to the conservative treatment regimen used in this study.

Hence, the results of this study refine the system of indications for conservative treatment of early-stage androgenetic alopecia [17], including identifying the types of treatment course when this approach is most effective.

Adverse events

No adverse events were documented.

Discussion

Summary of the primary outcome of the study

A combination of findings demonstrates that two alternative hair loss patterns objectively exist in males

Table 3. The dynamics in trichograms and phototrichograms in patients with different hair loss patterns (F2 and F3) after conservative therapy with topical minoxidil in combination with personalized micronutrient correction
Таблица 3. Изменение трихограмм и фототрихограмм у пациентов с различными паттернами утраты волос (F2 и F3) после проведения консервативной терапии

Scalp region	Parameter analyzed (Δ before and after completion of the therapy course)	Subgroup F2 (n = 27)	Subgroup F3 (n = 20)
Parietal	Hair density [number of hairs per cm2]	+21.50*	+15.61
	Hair diameter [μm]	+5.90***	+2.83
	Proportion of anagen hair, %	+10.03**	+8.06
	Proportion of telogen hair, %	–9.80**	–7.89
Occipital	Hair density [number of hairs per cm2]	+18.87	+9.56
	Hair diameter [μm]	+3.00	+0.94
	Proportion of anagen hair, %	+6.09**	+1.39
	Proportion of telogen hair, %	–5.04*	–1.33

The differences are significant: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
Различия достоверны: * $p < 0,05$; ** $p < 0,01$; *** $p < 0,001$.

with early-stage androgenetic alopecia, which differ in terms of their trichogram characteristics, mechanisms of pathogenesis, and response to conservative treatment.

Discussion of the primary outcome of the study

Analysis of the trichogram and phototrichogram data recorded during primary examination of patients with early-stage androgenetic alopecia showed that there are two variants of this disease consisting in nonuniform changes in hair density and diameter in the parietal and occipital scalp regions detected in 57.4% and 42.6% of the analyzed sample, respectively. Calculation of the relative HDp/HDo [14] and Dp/Do [13] values is an informative tool for differentiating these conditions providing additional information to macroscopic follow-up of the pattern of changes in patient's hair that identifies these ratios in partially overlapping ranges 0.61–1.14 and 0.67–1.00 for patients with the parietal hair loss pattern and 0.46–0.76 and 0.53–0.81 for patients with the occipital hair loss pattern.

The subsequent analysis of the pathogenetic mechanisms responsible for hair loss in individual scalp regions revealed that the hormonal factor plays a key role. It was most significant in the parietal region, where the presence of 5α-reductase and androgen receptor in hair follicles is considered to be most pronounced [18]. In turn, the results of the study demonstrating that the dihydrotestosterone level is simultaneously accompanied by a decline in total testosterone level as a result of its conversion by 5α-reductase in patients with parietal hair loss pattern strengthen the views on the androgen-dependent mechanism of this condition, while the occipital pattern proved to be androgen-independent and was associated with a slight increase in 17-OH-progesterone level only. Therefore, our findings make it possible to recommend measuring the dihydrotestosterone level as a laboratory test discerning the different types of disease course: when it exceeds the reference range (250–990 pg/mL), it can be considered an additional criterion for classifying the patient as belonging to the subgroup of patients with androgen-dependent alopecia with preferential involvement of the parietal scalp region.

In this context, the numerous changes in the micronutrient and vitamin status were not associated with isolated variants of androgenetic alopecia course, but were characteristic of all the observed cases of early-stage disease, which simultaneously was an indication for personalized correction of these deficiencies and using 5% minoxidil in combination with the basic topical treatment. Our earlier findings suggest that supplements containing Fe, vitamin E and folic acid, whose normalization in plasma directly correlates with hair restoration, are the most effective correction tools [17].

In the context of this study, it is fundamentally important that response to conservative therapy was significantly different in patients with the parietal and occipital hair loss patterns and developed nonuniformly in the scalp regions being compared. The strongest positive effect of treatment, which consisted in statistically significant increase in hair density and diameter, was observed for the parietal region for patients with the parietal hair loss pattern at baseline; for them, favorable changes in the ratio between anagen and telogen hair were also detected both in the parietal and occipital scalp regions. Hence, our data attest to the pathogenetic adequacy and well-proved clinical effectiveness of this approach; at early stages of androgenetic alopecia in men, indications for its use include the parietal hair loss pattern with the characteristic HDp/HDo and Dp/Do values, as well as an elevated dihydrotestosterone level, in addition to the previously identified positive predictor of conservation therapy: plasma level of Zr being > 10 μmol/L [19]. Meanwhile, the same response in patients with the occipital hair loss pattern was obviously insufficient, thus necessitating deeper analysis of the mechanisms of development of this condition and search for pathogenetically justified tools for its conservation treatment.

Study limitations

The study into the genetic factors was confined to five SNPs whose role in the development of androgenetic alopecia had been proved previously, which did not allow us to identify their role in identifying the parietal or occipital hair loss patterns at early stages of this disease. This problem can be solved by conducting large-scale screening of SNPs aiming to identify genomic associations that are characteristic of pathological hair loss in separate scalp regions and are possibly related to the androgen-dependent and androgen-independent mechanisms of development and differentiation of hair follicle cells.

Conclusions

The findings obtained in this study indicate that there are two variants of the course of early-stage androgenetic alopecia in men, which consist in preferential hair loss in the parietal or occipital scalp regions. The hormonal factor (increased dihydrotestosterone level and simultaneous decline in total testosterone level as a result on 5α-reductase activity) was shown to play a role for patients with the parietal hair loss pattern, whereas changes in the hormonal status in patients with the occipital hair loss status were confined to moderate elevation of 17-OH-progesterone level. Furthermore, multiple mineral and vitamin deficiencies have been proved to be important non-genetic factors for the development of androgenetic alopecia, which justified their personalized correction in addition to conservative treatment of this disease. The therapy course (topical application of minoxidil) in combination with micronutrient supplementation led to effective hair restoration in patients with the androgen-dependent parietal hair loss pattern. Meanwhile, patients with androgen-independent occipital hair loss pattern were resistant to this treatment, which makes it necessary to continue research into the pathogenetic mechanisms of this variant of androgenetic alopecia as well as search for tools for hair restoration in the occipital scalp region.

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