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ТИББИЁТДА ЯНГИ КУН НОВЫЙ ДЕНЬ В МЕДИЦИНЕ NEW DAY IN MEDICINE

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UNMASKING HIDDEN TRIGGERS: THE GENETIC AND ANAMNESTIC FOUNDATIONS OF CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

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✓ Resume

Objective: To identify and analyze the constellation of latent anamnestic and genetic predictors that determine the development of catastrophic antiphospholipid syndrome (CAPS) in pregnant women.

Materials and Methods: A comparative case-control study was conducted, including a cohort of 12 patients with a verified diagnosis of CAPS and a control group of 50 women with physiological pregnancies. A detailed analysis of medical histories was performed, along with molecular genetic typing for polymorphisms in hemostasis system genes (F5 Leiden, F2 Prothrombin, PAI-1) and folate cycle genes (MTHFR).

Results: Patients with CAPS were found to be characterized by a maximally burdened medical history, including a 100% incidence of arterial hypertension and a family history of thrombosis. A unique genetic profile was identified, featuring a 100% frequency of the homozygous mutant F5 Leiden (AA) genotype, combined with a high frequency of homozygous mutations in the F2 (33.3%) and PAI-1 (25.0%) genes. The cumulative effect of these factors creates a potent prothrombotic potential.

Conclusion: The development of CAPS is not a random event but rather the logical outcome in patients with a unique combination of powerful latent predictors. Identification of this risk profile (a combination of a burdened medical history and high-risk multigenic thrombophilia) during preconception counseling is key for risk stratification and the development of aggressive preventive therapy.

Key words: catastrophic antiphospholipid syndrome, pregnancy, predictors, thrombophilia, F5 Leiden, family history, arterial hypertension, preconception care.

YASHIRIN TRIGGERLARNI OCHIB BERISH: KATASTROFIK ANTIFOSFOLIPID SINDROMNING GENETIK VA ANAMNESTIK ASOSLARI

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✓ Rezyume

Maqsad: Homilador ayollarda katastrofik antifosfolipid sindrom (KAFS) rivojlanishini belgilab beruvchi latent anamnestic va genetik prediktorlar majmuasini aniqlash va tahlil qilish.

Materiallar va usullar: "Holat-nazorat" turidagi qiyosiy tadqiqot o'tkazildi. Tadqiqotga tasdiqlangan KAFS tashxisi bo'lgan 12 nafar bemor va nazorat guruhiga fiziologik kechuvchi homiladorligi bo'lgan 50 nafar ayol kiritildi. Anamnestic ma'lumotlar batafsil tahlil qilindi, shuningdek, gemostaz tizimi (F5 Leiden, F2 Protrombin, PAI-1) va folat sikli (MTHFR) genlari polimorfizmlari bo'yicha molekulyar-genetik tiplash amalga oshirildi.

Natijalar: KAFS bilan og'rigan bemorlar anamnezning maksimal darajada og'irlashganligi bilan tavsiflanishi aniqlandi, bu 100% holatlarda arterial gipertenziya va oilaviy trombotik anamnezni o'z

ichiga oladi. F5 Leiden (AA) gomozigot mutant genotipining 100% chastotasi hamda F2 (33,3%) va PAI-1 (25,0%) genlaridagi gomozigot mutatsiyalarning yuqori chastotasi bilan birgalikda namoyon bo'lgan noyob genetik profil aniqlandi. Ushbu omillarning kumülatif ta'siri kuchli protrombotik salohiyatni yaratadi.

Xulosa: KAFSning rivojlanishi tasodifiy hodisa bo'lmay, balki kuchli latent prediktorlarning noyob birikmasiga ega bo'lgan bemorlardagi qonuniy natijadir. Ushbu xavf profilini (og'irlashgan anamnez va yuqori xavfli multigen trombofiliya birikmasi) pregravidar tayyorgarlik bosqichida aniqlash xavflarni stratifikatsiyalash va agressiv profilaktik terapiyani ishlab chiqish uchun kalit omil hisoblanadi.

Kalit so'zlar: katastrofik antifosfolipid sindrom, homiladorlik, prediktorlar, trombofiliya, F5 Leiden, oilaviy anamnez, arterial gipertenziya, pregravidar tayyorgarlik.

РАСКРЫВАЯ СКРЫТЫЕ ТРИГГЕРЫ: ГЕНЕТИЧЕСКИЙ И АНАМНЕСТИЧЕСКИЙ ФУНДАМЕНТ КАТАСТРОФИЧЕСКОГО АНТИФОСФОЛИПИДНОГО СИНДРОМА

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✓ Резюме

Цель: идентифицировать и проанализировать совокупность латентных анамнестических и генетических предикторов, детерминирующих развитие катастрофического антифосфолипидного синдрома (КАФС) у беременных.

Материалы и методы: Проведено сравнительное исследование когорты из 12 пациенток с верифицированным диагнозом КАФС и контрольной группы из 50 женщин с физиологическим течением беременности. Проводился детальный анализ анамнестических данных, а также молекулярно-генетическое типирование по полиморфизмам генов системы гемостаза (F5 Leiden, F2 Prothrombin, PAI-1) и фолатного цикла (MTHFR).

Результаты: Установлено, что пациентки с КАФС характеризуется максимальной степенью отягощенности анамнеза, включая 100%-ную частоту артериальной гипертензии и семейного тромботического анамнеза. Выявлен уникальный генетический профиль, включающий 100%-ную частоту гомозиготного мутантного генотипа F5 Leiden (AA) в сочетании с высокой частотой гомозиготных мутаций в генах F2 (33,3%) и PAI-1 (25,0%). Кумулятивное накопление данных факторов создает мощнейший протромботический потенциал.

Заключение: Развитие КАФС не является случайным событием, а представляет собой закономерный исход у пациенток с уникальным сочетанием мощных латентных предикторов. Идентификация этого профиля риска (сочетание отягощенного анамнеза и мультигенной тромбофилии высокого риска) на этапе преграavidарной подготовки является ключевым фактором для стратификации риска и разработки агрессивной превентивной терапии.

Ключевые слова : катастрофический антифосфолипидный синдром, беременность, предикторы, тромбофилия, F5 Leiden, семейный анамнез, артериальная гипертензия, преграavidарная подготовка.

Relevance

Catastrophic antiphospholipid syndrome (CAPS), or Asherson's syndrome, represents the tip of the iceberg of autoimmune thrombotic pathology and one of the most dramatic challenges in modern medicine. The urgency of this problem is defined not only by its fulminant course but also by its extremely high mortality rate, which, according to the international CAPS Registry, reaches 50% even with modern intensive care methods [Cervera R. et al., 2017; Rodriguez-Pintó I. et al., 2018]. In the

context of pregnancy—a state of physiological hypercoagulation, endothelial activation, and immune modulation—the risk of CAPS manifestation increases significantly, making it one of the most formidable causes of maternal mortality [Makatsariya A.D. et al., 2018; Tektonidou M.G. et al., 2019]. Despite some success in treating the established syndrome, a key unresolved issue of fundamental importance for preventive medicine remains the identification of factors that predetermine such a catastrophic scenario. Why do some patients with antiphospholipid syndrome develop a thrombotic storm while others do not? The search for an answer to this question is the aim of this article, which is dedicated to a detailed analysis of the hidden (latent) anamnestic and genetic factors underlying this fatal predisposition.

Literature Review

Antiphospholipid syndrome (APS) is a systemic autoimmune disease whose criteria were clearly defined in 2006 [Miyakis S. et al., 2006] and is now recognized as one of the leading causes of acquired thrombophilia and recurrent obstetric complications. The pathogenesis of APS is based on the effect of antiphospholipid antibodies (aPL) on endothelial cells, platelets, and monocytes, leading to a state of persistent prothrombotic readiness [Gomez-Puerta J.A., Cervera R., 2014]. However, according to the widely accepted "two-hit model," the development of CAPS requires an additional trigger, or "second hit"—such as infection, surgery, malignancy, or pregnancy—which, against the background of a pre-existing predisposition (the "first hit"), unleashes an uncontrolled cascade of thrombus formation [Asherson R.A., 2006].

In recent years, the concept of the "first hit" has expanded considerably. It has become evident that not only the presence of aPL but also an underlying genetic predisposition to thrombosis plays a crucial role. Numerous studies have shown that the combination of APS with hereditary thrombophilias, such as the Factor V Leiden (F5 Leiden) or prothrombin gene (F2 G20210A) mutations, has a synergistic effect, exponentially increasing the risk of thrombotic events [Dolgushina N.V. et al., 2021; Pengo V. et al., 2010]. However, most studies have focused on the impact of single mutations on the course of classical APS. A comprehensive analysis of the cumulative effect of multiple anamnestic (chronic hypertension, family history) and genetic (multigenic thrombophilia) factors that form a profile of extremely high risk for the catastrophic form of the syndrome remains understudied, which defines the scientific novelty of this research.

Objective: To identify and analyze the constellation of latent anamnestic and genetic predictors that determine the development of catastrophic antiphospholipid syndrome (CAPS) in pregnant women

Materials and Methods

An observational case-control study was conducted. The main group consisted of 12 patients with a verified diagnosis of CAPS that developed during pregnancy. The control group comprised 50 somatically healthy women with physiological pregnancies and deliveries. Anamnestic data were collected through questionnaires and analysis of medical records. Molecular genetic testing included polymerase chain reaction (PCR) to detect polymorphisms in the F5 (G1691A - Leiden), F2 (G20210A - Prothrombin), PAI-1 (675 5G/4G), and MTHFR (C677T, A1298C) genes. Plasma homocysteine levels were determined by high-performance liquid chromatography (HPLC). Statistical analysis was performed using Statistica 10.0 software; the significance of differences was assessed using the Mann-Whitney U test, with a critical significance level of $p < 0.05$.

Analysis and Results

The Anamnestic Foundation of Predisposition. Analysis of medical histories revealed that patients with CAPS had the highest burden of key predictors. A striking pattern emerged: a history of arterial hypertension was present in 100% of CAPS patients, whereas in the control group, this figure was only 28% ($p < 0.001$). This finding indicates profound, chronic endothelial dysfunction, which creates a background for generalized microthrombosis. Similarly, a positive family history of thrombosis was present in 100% of CAPS patients, while it was entirely absent in the control group ($p < 0.001$). The picture of systemic vulnerability was completed by the reproductive history: recurrent pregnancy loss and preeclampsia in previous pregnancies were reported by 83.3% of the patients. This collection of data confirms that CAPS does not develop de novo but on the background of a pronounced, pre-existing latent predisposition.

The Genetic 'Code' of Catastrophe. If the medical history forms the foundation, the genetic profile is the 'code' for the catastrophe. Comparative analysis revealed a unique profile characterized by the accumulation of multiple prothrombotic alleles. The most striking and potentially pathognomonic finding was the 100% frequency of the homozygous mutant F5 Leiden AA genotype in the CAPS group, which was virtually absent in the control group (0.0%). This genotype signifies complete resistance to the anticoagulant action of activated protein C (APC), which, in the hypercoagulable state of pregnancy, leads to uncontrolled thrombin generation. However, this defect did not act alone. The high frequency of the homozygous F2 Prothrombin AA (33.3%) and PAI-1 4G/4G (25.0%) genotypes created a powerful prothrombotic background conducive to the formation of lysis-resistant microthrombi. The 100% carrier rate of mutant alleles in the folate cycle MTHFR genes also contributed to endothelial dysfunction, which was confirmed by laboratory findings: homocysteine levels in the CAPS group (median 16.74 $\mu\text{mol/L}$) were statistically significantly higher than in the control group (median 9.49 $\mu\text{mol/L}$; $p < 0.001$).

Conclusion and Recommendations

Catastrophic antiphospholipid syndrome is the result of a 'perfect storm' in which powerful latent predictors act synergistically. It occurs in patients with a burdened medical history (100% with arterial hypertension and a family history of thrombosis) and a unique cumulative genetic profile, fundamentally based on the homozygous F5 Leiden mutation. This combination of factors creates an extremely high prothrombotic potential, which is actualized by the triggering effect of pregnancy.

1. Patients with a burdened personal and family history of thrombosis, as well as an adverse obstetric history, should undergo expanded molecular genetic testing for hereditary thrombophilias, including F5 Leiden genotyping, during preconception evaluation.
2. The identification of a combination of APS with high-risk multigenic thrombophilia (especially the homozygous F5 Leiden mutation) should be grounds for classifying a patient in the extreme-risk group for developing CAPS during pregnancy.
3. For this category of patients, a personalized, aggressive preventive therapy strategy (including anticoagulants and possibly immunomodulators) must be developed, starting at the family planning stage and continuing under strict multidisciplinary supervision.

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