Personalized Psychiatry and Neurology

Case report

The Personalized Algorithm of the "Tension-Type Headache and Arterial Hypertension" Phenotype Diagnosis

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Abstract: The tension-type headache (TTH) and arterial hypertension (AH) are one of the most common conditions worldwide. The cumulative assessment of clinical and genetic predictors needs to be revised. The aim is designing a scale and algorithm for predicting the risk of the "TTH + AH" phenotype developing in outpatient clinics. The leading non-genetic predictors are emotional lability and personal uneasiness. The leading genetic predictor is the carriage of the minor T allele and the heterozygous CT genotype rs3782218, as well as heterozygous genotype GA rs7314935 of the *NOS1* gene encoding neuronal nitric oxide synthase. There are scale and personalized algorithm for assessing the risk of the "TTH + AH" phenotype development. There is the higher the score, the higher the risk of "TTH + AH" phenotype development in hypertensive patients. The using of the presented scale and algorithm will allow timely identification of a risk group for the "TTH + AH" phenotype and avoid diagnostic errors.

Keywords: *tension-type headache; arterial hypertension; comorbidity; development risk assessment; algorithm; anxiety; obesity; nNOS; NOS1; genetic biomarker; rs3782218; rs7314935*.

Introduction

The tension-type headache (TTH) and arterial hypertension (AH) are one of the most common conditions worldwide [1]. The problem of the relationship between TTH and AH is relevant, since these diseases can aggravate each other, forming a complex clinical phenotype or overlap syndrome "TTH + AH". This comorbidity occurs frequently in the clinical practice of family doctors, therapists, neurologists and cardiologists. Many studies show the higher risk of developing AH in TTH patients and higher risk of developing TTH in hypertensive patients [2]. So, on average 85% of hypertensive patients complain of headache, and 30% of patients with headache have AH. Moreover, among patients with TTH the probability of AH is higher (55-85%) than among patients with migraine [1].

Despite the presence in the latest edition of the International Classification of Headaches of the third revision (ICHD-III, 2018) the clear criteria for diagnosing TTH [3], the concept of "hypertensive headache" still exists. On the one hand, primary care physicians make mistakes in the differential diagnosis of TTH and secondary headaches in patients with AH. On the other hand, patients with AH often rely on the presence of a headache as a criterion for assessing their blood pressure (BP) level without using a tonometer.

Headache in hypertensive patients can either be primary (more often it is TTH, in which case this pathological condition is comorbid for AH, and there is the clinical phenotype "TTH + AH"); or secondary (often abused against the prolonged excessive intake of non-steroidal anti-inflammatory drugs and / or antihypertensive drugs; less often – a headache attributed to disorder of homoeostasis against the hypertensive crisis) [2].

The cumulative assessment of the contribution of clinical (exogenous and endogenous) and genetic predictors (biomarkers) needs to be revised. Thus, the development of

a personalized approach to predicting the risk of development and diagnosing the clinical phenotype "TTH + AH" is an urgent problem in neurology and therapy from the standpoint of rapidly developing personalized medicine.

Objective

The aim is designing a scale and algorithm for predicting the risk of the "TTH + AH" clinical phenotype developing in outpatient clinics of the relevant profiles (family medicine, internal medicine, neurology and cardiology), as well as a decision-making strategy for managing patients with AH.

Materials and Methods

Conception

These scale and algorithm are results of the comprehensive study on the topic "Clinical and genetic predictors of the tension-type headache and arterial hypertension phenotype", registration No. 122030300108-6 dated March 03, 2022. During the project, 91 patients were comprehensively examined. Neurological and cardiological observations, neuropsychological testing and molecular genetic testing were carried out, aimed at finding clinical and genetic predictors of the "TTH + AH" phenotype development.

The study was performed in accordance with the standards of good clinical practice and the principles of the Declaration of Helsinki. Study material was obtained after approval of the local ethics committee of the V.F. Voino-Yasenetsky Krasnoyarsk State Medical University (KrasSMU), protocol No. 101/2020 dated October 31, 2020.

The study was supported by the intra-university grant to support the research of young scientists of the KrasSMU (No. 462-base dated July 12, 2021).

The participant signed a voluntary informed consent. The patient did not receive any remuneration for participating in the clinical trial. Researchers did not receive any remuneration for conducting clinical trials.

Patient Observation

TTH was diagnosed with by a neurologist according to the ICHD-III criteria [3]. AH was diagnosed by a cardiologist according to the European Society of Cardiology and the European Society of Hypertension (2018) criteria [4] and the Russian Society of Cardiology (2020) criteria [5].

In the study of the somatic status, morphometry was carried out: height (centimeters, cm) and weight (kilograms, kg) using calibrated devices, waist circumference (in cm) using a centimeter tape. The body mass index (BMI) was calculated using the Quetelet formula: BMI = body weight (kg) divided by the growth rate (meters) squared; and measured, respectively, in kg/m^2.

Measurement of systolic BP / diastolic BP on the arm was carried out for each patient. The measurement was carried out with a manual sphygmomanometer at rest after a 5-minute rest. The measurement was carried out with the patient in a sitting position. Three measurements were taken on each arm (with an interval of 2 min). The smaller of the last two measurements was taken as the final (recorded) value.

Neuropsychological Testing

Participants in the study underwent neuropsychological testing of anxiety and depression [6]. The following scales were used: Spielberger questionnaire, Scale of emotional excitability, Scale "Self-assessment of anxiety, frustration, aggressiveness and rigidity", Beck Depression and Anxiety Scale, Hospital Depression and Anxiety Scale.

Molecular Genetic Testing

Genetic profiling was used based on the profile of patient (homo- and heterozygous carriers of risk alleles of single-nucleotide variants (SNVs) of the *NOS1*, *NOS2*, *NOS3* genes encoding neuronal nitric oxide synthases (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) [7, 8, 9, 10].

TaqMan® quantitative Real-Time Polymerase Chain Reaction (RT-PCR) (Applied Biosystems, Foster City, CA, USA) was used to determine the genotype of the 6 SNVs [7]: rs3782218 (chr12:117771511 C>T) and rs7314935 (chr12:117718837 G>A) of the *NOS1* gene; rs2779249 (chr17:26128581 C>A) and rs2297518 (chr17:26096597 G>A) of the *NOS2* gene; rs1799983 (chr7:150696111 G>T) and rs2070744 (chr7:150690079 T>C) of the *NOS3* gene using diagnostic equipment Rotor-Gene 6000 (Corbett Life Science, Australia) and technology allelic discrimination of TaqMan and fluorescent probes (Applied Biosystems, USA).

Results

Non-genetic and Genetic Predictors of the "Tension-Type Headache and Arterial Hypertension" Phenotype

According to the results of our study "Clinical and genetic predictors of the tension-type headache and arterial hypertension phenotype", statistically significant non-genetic predictors (risk factors) for the development of the "TTH + AH" phenotype are: low physical activity of hypertensive patients (43.3%, $p = 0.047$); obesity of the second and third severity (26.7%, $p = 0.01$ and 16.7%, $p = 0.018$).

The main triggers for TTH episodes in patients with AH are stress (77.3%) and postural tension (66.7%). An increase in BP is a trigger for an episode of TTH in patients with "TTH + AH" phenotype in only 10% of cases. Psycho-emotional stress (55%) is the main trigger for increased BP in patients with the "TTH + AH" phenotype. An episode of severe TTH is often an additional trigger for an increase in BP (60.0%, $p = 0.002$).

The leading non-genetic predictors of the "TTH + AH" phenotype development in hypertensive patients is emotional lability (26.3%, $p = 0.039$) and personal uneasiness (47.4%, $p = 0.018$). A high level of anxiety (42.2%, $p = 0.017$) and situational uneasiness (36.8%, $p = 0.021$) in response to stress factors are the main triggers for the "TTH + AH" phenotype development.

The leading genetic predictors of the "TTH + AH" phenotype development are the carriage of the minor T allele (odds ratio (OR) = 22.18; 95% confidence interval (CI) 2.84 – 173.54) and the heterozygous CT genotype (OR = 20.0; 95% CI 2.4 – 166.97) of SNV rs3782218 [8], as well as heterozygous GA genotype (OR = 3.47; 95% CI 1.04 – 11.56) of SNV rs7314935 of the *NOS1* gene encoding nNOS, which is expressed in the endothelium of cerebral and peripheral vessels, transversely striated muscles and the nociceptive system of the brain [11].

Assessment of the Risk of the "Tension-Type Headache and Arterial Hypertension" Phenotype

We have developed a scoring scale for non-genetic and genetic predictors of "TTH + AH" phenotype development in hypertensive patients (Table 1).

As shown in Table 1, the greater the significance of the studied non-genetic and/or genetic predictors, the higher the risk of "TTH + AH" phenotype development. Patients with AH with a total score up to 5 points have a low risk of "TTH + AH" phenotype development, while patients with AH with a total score more than 9 points have a high risk. The higher the score, the higher the risk of "TTH + AH" phenotype development in hypertensive patients. In addition to the scale presented above, a personalized algorithm was developed to predict the risk of "TTH + AH" phenotype development in hypertensive patients (Figure 1).

Table 1. Scale for assessing the risk of the "tension-type headache and arterial hypertension" phenotype development.

Predictor	Evaluation criterion	Comment
Physical activity level: - habitual load (Intense or moderate) - periodic load (Intense or moderate) - low activity	 0 points + 1 point + 2 points	Moderate physical activity - a load that can be sustained for 60 minutes, intensive - 30 minutes. It is considered habitual: moderate - min 150 min per week; intensive – min 75 min per week.
Obesity: - normal body weight - overweight - first degree - second degree - third degree	 - 1 point 0 points + 1 point + 2 points + 2 points	On body mass index: normal body weight - 20-24.9 kg/m^2 overweight - 25-29.9 kg/m^2 first degree - 30-34.9 kg/m^2 second degree - 35-39.9 kg/m^2 third degree - ≥ 40 kg/m^2
Emotional lability - low - average - high - very high	 - 1 point 0 points + 1 point + 2 points	On the Scale of emotional excitability: low - 0-7 points; average - 8-13 points; high - 14-17 points; very high - 18-20 points
The level of personal anxiety(uneasiness) - short - moderate - high	 0 points + 1 point + 2 points	On the Spielberger scale: low - 0-30 points moderate - 31-45 points high - 46-80 points
Carriage of allelic variants rs3782218 of the *NOS1* gene - CC - CT - TT	 0 points + 2 points + 4 points	 CC – homozygous dominant genotype CT – heterozygous genotype TT – homozygous recessive genotype
Carriage of allelic variants rs7314935 of the *NOS1* gene - GG - GA - AA	 0 points + 1 point + 2 points	 GG – homozygous dominant genotype GA – heterozygous genotype AA – homozygous recessive genotype

Note: Summary of scores from 0 to 5 – low risk of "TTH + AH" phenotype development;
6-8 points – middle risk of "TTH + AH" phenotype development;
9-14 points - high risk of "TTH + AH" phenotype development.

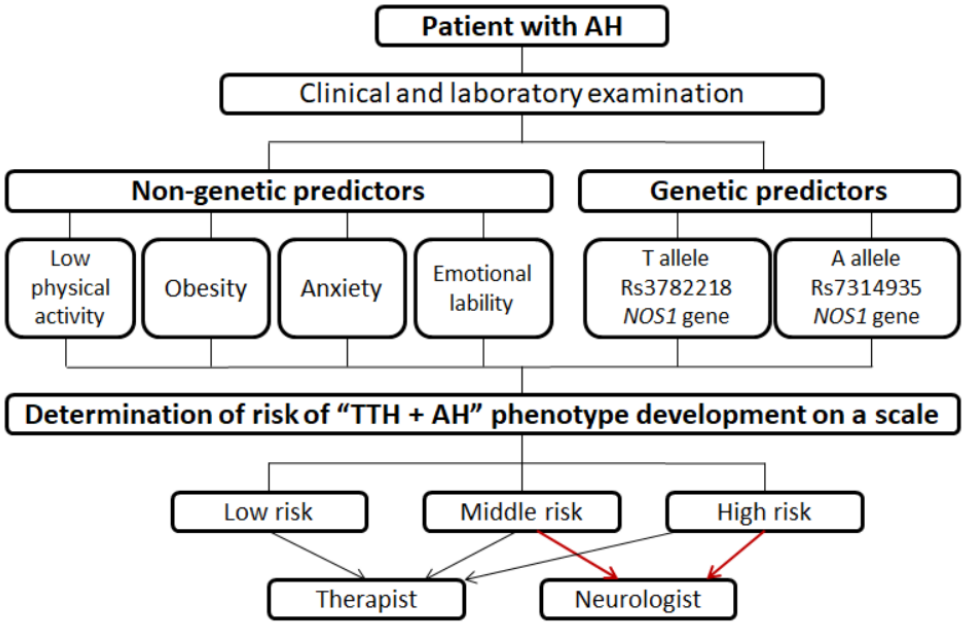

Figure 1. The personalized algorithm of risk assessment of the "tension-type headache and arterial hypertension" phenotype development.

Discussion

According to this algorithm, all patients with AH on an outpatient basis are recommended to be examined to identify and evaluate non-genetic predictors of the "TTH + AH" phenotype development, including determination of the level of daily physical activity, anthropometry, neuropsychological testing of emotional lability and anxiety. In case of obtaining high scores on the above scale and determining the middle risk (from 6 to 8 points) based on the assessment of non-genetic predictors, it is recommended to additionally conduct molecular genetic testing of genetic predictors (T allele of rs3782218 and A allele of rs7314935 of the *NOS1* gene) with a high risk of "TTH + AH" phenotype development.

When determining the middle or high risk of "TTH + AH" phenotype development, a patient with AH is recommended to be observed not only by a general practitioner (or cardiologist), but also by a neurologist. An interdisciplinary approach to this phenotype is important to the selection of rational pharmacotherapy for TTH and AH, taking into account the drug-drug interaction of non-steroidal anti-inflammatory drugs and antihypertensive drugs and their potential to provoke an increase in BP and headache episode, respectively [2].

It is important to consider the identifying genetic predictors when choosing pharmacotherapy for the phenotype. It is recommended to choose drugs that do not affect the common pathophysiological mechanism of the TTH and AH development, namely, the violation of NO synthesis.

Also, these scale and algorithm may be to optimize the pedagogical process at the departments of neurology, therapy and general medical practice involved in the continual medical education.

Conclusions

Thus, the using of the presented scale and a personalized algorithm will allow timely identification of a risk group for the "TTH + AH" phenotype development and avoid diagnostic errors. The introduction of the developed scale and algorithm in patients with a high risk of developing the phenotype "TTH + AH" into the real medical practice may allow personalizing the tactics of managing this phenotype at the outpatient stage. This, in turn, may reduce the risk of an unfavorable course of the phenotype and avoid its cerebrovascular and cardiovascular complications, as well as the risk of medication overuse headache.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of V.F. Voino-Yasenetsky Krasnoyarsk State Medical University (protocol code No. 101/2020 dated October 31, 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

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Conflicts of Interest: The author declares no conflict of interest.

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