Study of the incidence of hyperuricemia in young males' population with rapid entry into the plateau of 4 500m

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Abstract

Objective: To study the incidence and risk factors of hyperuricemia in young males who rapid entered into the plateau of 4 500 m. **Methods:** The study contained 390 males aged 18-35 years (21.6 ± 2.5 years), who rapidly entered the plateau with an altitude of 4 500 m. According to their basic level of uric acid (UA), they were divided into two groups, high uric acid (HUA) group and normal uric acid (NUA) group. The characteristics and physiological index, such as the body weight and the height, of them were recorded. For the test of the biochemical indicators, the venous blood samples were collected at the altitude of 4 500 m in the morning. The count of blood cells, blood urea nitrogen (BUN), serum creatinine (SCR), lactate dehydrogenase (LDH), total bilirubin (TBIL), direct bilirubin (DBIL) and indirect bilirubin (IDBIL) were compared between the two groups. **Results:** The incidence of hyperuricemia was 65.1% (254/390) at 4 500 m. At the altitude of 4 500 m, the mean hemoglobin concentration (MCHC) of red blood cells in the HUA group was significantly lower than that in the NUA group. Hemoglobin (HGB), mean red blood cell volume (MCV), TBIL, IDBIL, BUN, SCR and LDH in the HUA group were significantly higher than those in the NUA group, though without statistically significant differences in the other variables. Meanwhile, multivariate analysis showed at the altitude of 4 500 m, the risk of HUA increased by 0.982, 1.038 and 1.045 times when MCHC decreased by one unit and TBIL and SCR increased by one unit, respectively. **Conclusion:** The incidence of hyperuricemia was high of 65.1% rush entry into the plateau of young male. Decreased MCHC and elevated TBIL and SCR were independent risk factors for hyperuricemia when rapid enter into 4 500 m.

Keywords

rapid entry; the plateau; hyperuricemia; renal function

Received 12 May 2021, accepted 15 October 2021

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1 Introduction

Uric acid(UA) was the final product of purine metabolism in the circulatory system and associated hyperuricemia is closely correlated with a series of diseases such as cardiovascular and kidney diseases. In China, high uric acid (HUA) is defined as the level of serum uric acid (SUA) beyond $420 \mu\text{mol/L}$, according to the consensus of Chinese experts in 2017^[1]. Till now, thousands of studies investigated that besides gout, the metabolism disorders of UA is associated with the development of renal dysfunction, endocrine metabolism disorders and cardiovascular and cerebrovascular diseases^[2-13] and it may even induce or aggravate cancer^[3]. Due to the special geographical environment, the retrospective studies showed that prevalence rate of hyperuricemia is generally higher in the plateau area than that in the plain area^[1].

However, for those who rapidly enters into the plateau especially areas higher than 3 500 m, few studies focus on the alterations of the level of UA and other biochemical index, as well as the relationship between them. To explore the incidence and risk factors of hyperuricemia in population with rapid entry into the plateau, young males from sea level and rushing into 4 500 m were enrolled in the present study. The present study aims to investigate the incidence of hyperuricemia and its epidemiological characteristics after rapid entry into the plateau of 4 500 m.

2 Data and methods

2.1 Study objects

A total of 390 young men who rushed into the plateau of 4 500 m from June to July 2019 were included in this study, and informed

consents were got before the study. All participants were aged 18-35 (21.6 ± 2.5 years) and the diet and labor intensity are generally the same. The inclusion criteria include: constant adherence to the ascendant from sea level to high altitude, cooperate with blood collection and relevant questionnaire survey with full attendance. The exclusion criteria contain those who have severe altitude sickness, fail to provide complete data. Venous blood samples were collected from the people in the morning and contained in dry ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes. Counting of blood cells was made by automatic blood analyzer (Sysmex-XS-800i, Japan). The samples were centrifuged for 10 min at 3 500 RP and 0.5 mL of serum was collected for the assay of biochemical analysis by Beckman Coulter automatic biochemical analyzer. According to the basic level of UA tested on the sea level, the objects were divided into two groups, the normal uric acid (NUA) group ($SUA \leq 420 \mu\text{mol/L}$) and the high uric acid (HUA) group ($SUA > 420 \mu\text{mol/L}$). This study was approved by the Medical Ethics Committee of the Clinal Medical College in PLA Army Hospital, and informed consent in writing was provided by the legal guardians of the VPIs.

2.2 Statistical analysis

SPSS 22.0 was used for statistical analysis. The counting data

were compared with Chi-square test and results demonstrated as the number of cases (N) and percentage (%). Comparison between measurement data was performed by using Mann-Whitney U test and results shown as median (P25%, P75%). Univariate and multivariate logistic regression analysis were used to assess the factors affecting UA, and variables with obvious univariate significance were included in the multivariate analysis, in which stepwise regression was used to determine the collinearity among independent variables.

3 Results

3.1 The occurrence of HUA after rapid entry into the plateau of 4 500 m

Compared with those at the altitude of sea level, at 4 500 m, the incidence of HUA among 390 men was 65.1% (254/390), the Mean Corpuscular Hemoglobin Concentration (MCHC) levels in the HUA group were significantly lower than that in the NUA group. However, the levels of HGB, MCV, TBIL, IDBIL, BUN, SCR and LDH in the HUA group were all significantly increased (Table 1). Although no differences in red blood cell (RBC) and hemoglobin (HGB) were observed in both groups, they were higher at the altitude of 4 500 m than at the sea level.

Table 1 Clinical characteristics (at altitude of 4 500 m) of the objectives

Variables	HUA group (n = 254)	NUA group (n = 136)	Z value	P value
BMI	21.47(20.36, 23.06)	21.63 (20.24, 22.88)	-0.102	0.919
RBC	5.58 (5.49, 5.89)	5.76 (5.5, 5.93)	-1.286	0.185
HGB	161 (157, 175)	171 (162, 176)	-2.073	0.021 [*]
HCT	52 (49.6, 55.48)	54.0 (51.23, 56.12)	-1.971	0.041 [*]
MCV	94.9 (91.28, 99.43)	93.38 (87.66, 98.01)	-2.961	0.009 [*]
MCH	29.46 (28.75, 30.47)	30 (29.21, 31.04)	-0.861	0.407
MCHC	309 (302.45, 323.15)	323.4 (303.5, 336.4)	-4.127	<0.001 [*]
PLT	221.5 (191.75, 253)	222 (192, 253.5)	-0.168	0.891
PDW	16.8 (14.865, 18.6)	16.41 (14.7, 18.9)	-0.149	0.799
MPV	12.2 (11.3, 13.4)	12.6 (11.03, 13.5)	-0.296	0.734
PCT	0.28 (0.24, 0.32)	0.27 (0.24, 0.33)	-0.306	0.695
TBIL	14.96 (11.08, 19.96)	11.93 (9.04, 17.33)	-4.318	<0.001 [*]
DBIL	3.88 (2.76, 5.89)	3.76 (2.62, 5.01)	-1.974	0.056
IDBIL	10 (6.46, 14.37)	7.57 (5.51, 11.63)	-3.780	<0.001 [*]
BUN	6.6 (5.84, 7.7)	5.4 (4.16, 6.28)	-6.665	<0.001 [*]
SCR	100.54 (82.34, 116.37)	74.2 (68.3, 82.4)	-9.163	<0.001 [*]
LDH	232 (181.57, 276.5)	185.2 (142.35, 229)	-4.399	<0.001 [*]

* $P < 0.05$.

BMI: Body Mass Index; RBC: Red Blood Cell; HGB: Hemoglobin; HCT: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; PLT: Platelet; PDW: Platelet Distribution Width; MPV: Mean Platelet Volume; PCT: plateletocrit; TBIL: Total Bilirubin; DBIL: Direct Bilirubin; IDBIL: Indirect Bilirubin; BUN: Blood Urea Nitrogen; SCR: Serum Creatinine; LDH: Lactic Dehydrogenase.

3.2 Univariate and multivariate logistic regression analysis

At the altitude of 4 500 m, HGB, MCV, MCHC, TBIL, IDBIL, BUN, SCR and LDH were included in the multi-factor analysis in this study. The results showed that MCHC, TBIL and SCR were retained in the final model, and the risk of HUA increased by 0.982, 1.038 and 1.045 times when MCHC decreased by one unit and TBIL and SCR increased by one unit (Table 2).

Table 2 Logistic Regression analysis (4 500 m)

	Regression coefficient	Standard error	Wald statistics	P value	OR value
MCHC	-0.017	0.009	5.329	0.025	0.987
TBIL	0.034	0.019	4.565	0.036	1.041
SCR	0.045	0.005	55.728	<0.001	1.039

MCHC: Mean Corpuscular Hemoglobin Concentration;

TBIL: Total Bilirubin; SCR: Serum Creatinine

4 Discussion

UA metabolism in our body contains two pathways: the endogenous and exogenous ways, which indicates two different sources of SUA. 80% is produced from endogenous purine metabolism, including the synthesis of amino acids, phosphoribose, the other small molecular compounds and the catabolism of nucleic acids. 20% is produced by the metabolism of purine-rich foods and nucleic acid proteins. The main pathway for excretion of UA is through the kidney, which contains nearly 2/3. The remaining 1/3 of UA is excreted through the digestive tract and sweat. In kidney, UA is reabsorbed and secreted by the proximal renal tubules, and eventually absorbed, while the unabsorbed UA is excreted in the urine. The development of HUA usually caused by the increasing synthesis and/or decreased excretion.

The main problem when rapid entering into the plateau is hypoxia, which could induce a series of pathophysiological changes to the organism. For kidney, hypoxia could injury the UA filtration, renal tubule reabsorption, secretion and excretion, which directly affects the formation of UA gradient and UA excretion, resulting in increased SUA concentration in the body^[14]. The increased renal load and poor urate excretion, increasing urate deposition in renal tubules would further aggravate renal injury, as followed by the increased SUA levels^[15]. Furthermore, fatigue and lack of rest during rapid entry into the plateau can also affect SUA metabolism. However, at the initial stage, the increased SUA levels is a self-protective mechanism. The long-term high-level exposure to SUA in the

high altitude will further damage vascular endothelium and lead to metabolic disorders. Plateau environment with acute hypoxia may causes extensive renal hypoxia stress, mainly damaging glomerular endothelial cells and renal tubular epithelial cells, which cannot be recovered through reoxygenation^[16]. In our research, SCR in HUA group fluctuated within normal ranges, but the multivariate regression analysis showed that SCR was an independent risk factor for HUA. For those with abnormal SCR who need a rush entry into the plateau should be cautious for the level of UA.

During the duration of rush entry into 4 500 m, HGB and other associated indicators elevated to match normal oxygen delivery. Bone marrow hematopoietic stem cells were amplified and stored in quantity through proliferation to supplement the needs of downstream RBC. On the other hand, bone marrow hematopoietic stem cells also differentiated selectively to the erythroid in a larger proportion and preferentially generated more RBCs^[17]. Increased HUA also related to the hypoxia-induced secondary polycythemia in the plateau. Researchers revealed that serum UA contributes to more than 2/3 of the total antioxidant capacity of human body^[18]. The antioxidant effect of SUA may have a protective effect on RBC, and therefore a significantly positive correlation between SUA and RBC level in HUA patients was observed, indicating high SUA level would lead to increased RBC level in peripheral blood. The protective effect of SUA on RBC may be related to its direct antioxidant activity of inhibiting free radicals and reactive oxygen species, and thus SUA protects the smooth surface of RBC cell membrane and prevent the formation of spinous and spherical RBC^[19]. In the present research, although no statistically significant difference in RBC or HGB between the two groups was observed, both indexes were compensatory increased than the normal reference value at 4 500 m. However, different from previous literature results, our research showed that MCHC reduction is closely related to plateau HUA, which may be related to the fact that the compensatory function has not been fully established during the rapid advance to plateau.

Bilirubin is one of the end metabolic products of heme catalyzed by heme oxygenase-1 (HO-1). Traditionally, bilirubin is regarded as a toxic metabolic waste. However, with the deepening of research, it has been revealed that bilirubin is not only a strong endogenous antioxidant, but also has certain antioxidant and cell protective functions. In animal models such as endotoxemia and ischemia reperfusion, bilirubin has shown a series of anti-inflammatory effects^[20]. In the process of rush entry into high altitude, hypoxia can induce damages in liver function. In the early stage both TBIL and SUA were increased, serving as a self-protective mechanism during stress^[21]. The multivariate regression analysis showed that high serum TBIL levels are closely related to high HUA levels during

rapid entry into plateau. Thus, elevated TBIL may be one of the risk factors for plateau HUA.

The changes are significant for the human body after entering the plateau, contributing to our adaption of plateau environment and improving our survival ability. Therefore, the study on the changes of peripheral blood cells, blood biochemical indexes and other indexes provides significant reference for the prevention of altitude sickness. Some study revealed abundant cross-sectional or retrospective data on plains and plateaus. However, studies reporting the dynamic data involved with rapid entry from the altitude of 4 500 m were scarce. This study aims to explore the incidence of HUA and its associated risk factors in the population with rapid entry into the plateau. This study shows that decreased MCHC and increased TBIL and SCR are independent risk factors for HUA. However, the molecular

metabolisms involving how MCHC, bilirubin and SCR affect the purine metabolism of UA remains unclarified, rendering further investigation.

Ethical approval and informed consent

This study was approved by the Medical Ethics Committee of the Clinal Medical College in PLA Army Hospital (No.2021-88), and informed consent in writing was provided by the legal guardians of the VPIs.

Conflicts of interests

The authors have declared that they have no competing interest exists.

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