

The study of prevalence rate, and clinical characteristics of high altitude deterioration

S.-W. XIE, C. LIU, Y.-X. GAO, Y. CHEN, C.-H. JIANG, L. CHEN, Y.-Q. GAO

Institute of Medicine and Hygienic Equipment for High Altitude Region, College of High Altitude Military Medicine, Third Military Medical University, Key Laboratory of High Altitude Medicine, Ministry of Education, Chongqing, China

Abstract. – OBJECTIVE: This study was aimed to investigate the prevalence rate and clinical characteristics of high altitude deterioration (HADT), which would provide a scientific basis for the diagnosis and prevention of HADT.

SUBJECTS AND METHODS: A total of 175 subjects, who had migrated to a high altitude (4516 m) for more than 1 year, were investigated. A questionnaire survey based on the symptoms of HADT was conducted, and 117 subjects were determined to have HADT according to the diagnostic criteria of HADT. To explore the clinical characteristics of HADT, 117 HADT patients and 31 healthy individuals were assigned to HADT patient group and healthy control group, respectively. Their body mass indexes (BMIs), blood rheology, full blood count (including hemoglobin concentration, leukocyte count, neutrophil count, lymphocyte count and platelet count), blood pressure, heart rate, oxygen saturation as well as left ventricular ejection fraction (LVEF) and fraction shortening (LVFS) were assessed.

RESULTS: The prevalence rate of HADT was 66.9% at a high altitude of 4516 m. Compared with those in healthy people at high altitude, some health indicators such as BMI, leukocyte count, neutrophil count, lymphocyte count, platelet count, systolic blood pressure, oxygen saturation, LVEF value and LVFS value were lower but other indicators including the blood viscosity, hematocrit, hemoglobin concentration and heart rate were higher in patients with HADT.

CONCLUSIONS: The prevalence rate of HADT (66.9%) was high among people moving to a high altitude of 4516 m. Clinical characteristics of HADT were: (1) Impairment of left ventricular systolic function; (2) Immune depression; (3) Microcirculation disturbance; and (4) Decline of hemostasis and coagulation function.

Key Words:

HADT, Prevalence rate, Clinical characteristics.

Introduction

High altitude is a hostile environment. Physiological stress from hypoxia, cold, wind, danger-

ous ultraviolet (UV) rays from the sun, dehydration and a lack of antioxidant nutrients in the diet, all contribute to decreased physical and mental performance at high altitude¹. Some people who remain or live at a high altitude for prolonged periods of time will appear a series of symptoms including lethargy, impaired cognitive function, anorexia and weight loss. Milledge JS called this syndrome high altitude deterioration (HADT) et al². Chinese scholars officially named this syndrome as HADT in the Third Chinese National Symposium on High altitude Medicine Conference held in September 1995³, and proposed a diagnostic criteria: (1) HADT occurs in immigrants (Han Chinese) who live at an altitude of more than 3000 m above sea level for a long time, and in climbers who live at high altitude (> 5000 m above sea level) for a long time; (2) Mental deterioration is characterized by headache, dizziness, difficulty sleeping (insomnia), hypomnesia, hyposexia, decreased capability of thinking and judgment, emotional lability, and apathy; (3) Physical deterioration is characterized by anorexia, weight loss, fatigue, decreased working capacity, sexual disorders (dysfunction), and irregular menstruation; (4) Concomitant signs and symptoms include hypotension, hair loss, odontoptosis, koilonychia (spoon nails), intermittent edema, and slightly enlarged liver; (5) No erythrocytosis and significant pulmonary hypertension; (6) Course of the disease varies along time, which is characterized by undulatory changes in signs and symptoms, but gradually becomes severe, followed by sustained and progressive deterioration. The signs and symptoms are gradually improved or disappeared when patients move to a low-altitude or sea-level area.

An increased number of sea-level residents visit areas above 4000 m of altitude for recreational, religious, economic, and military purposes and they are at risk for experiencing some de-

gree of high-altitude deterioration. Despite the global popularity of recreating and residing at high altitude continues to increase, little is known about the prevalence rate and the clinical characteristics of HADT at high altitude. Therefore, this study was aimed to assess the prevalence rate of HADT and its clinical characteristics among people who immigrated to high altitude.

Subjects and Methods

Subjects

A total of 175 Han young men, who had immigrated to high altitude (4516 m), were investigated. All of the respondents were born in plain before they immigrated to high altitude, and had been confirmed healthy through physical examination. Among all 175 respondents, there were 117 patients with HADT. To explore the clinical characteristics of HADT, the participants were divided into two groups. One was experimental group consisting of 117 patients with HADT, while another one was control group consisting of 31 healthy individuals.

In this study, the inclusion criteria of the HADT were: 1. Immigrants who live at an altitude of > 3000 m above sea level for more than one year; 2. People who suffer decreased capability of thinking and judgment, and memory loss; 3. Hemoglobin concentration is less than 210 g/L; and 4. significant pulmonary hypertension (less than 50 mmHg).

Investigation of Symptoms of HADT and the Prevalence Rate of HADT

To investigate the main symptoms of HADT and the prevalence rate of HADT at high altitude, 175 people who had lived at a high altitude of 4516 m were asked to fill out a symptom questionnaires. This symptom questionnaire was designed to diagnose and collect symptoms of HADT according to the diagnostic criteria of HADT. It was based on the following symptoms: hypomnesia, hyporosexia, fatigue, anorexia, sleep disturbance, decreased working capacity, weight loss, catching cold easily, headache, hair loss, odontoptosis, koilonychia. This symptom questionnaire was not a scoring system that assessed HADT severity. It could be used only to diagnose and collect symptoms of HADT.

Baseline Characteristics of Patients with HADT

In order to know the baseline characteristics of the patients with HADT, the height, weight and age of the subjects were collected, and their body mass indexes (BMIs) were calculated from their weight (kg) and height (m) as weight/height².

Blood Rheology of Patients with HADT

To evaluate the index of blood rheology in the patients with HADT, the subjects were asked to fast overnight for 12 hours and their venous blood samples were collected in the morning for analysis of blood rheology index such as whole blood viscosity and hematocrit with an automatic blood rheometer (SH-212A, China).

Full Blood Count of Patients with HADT

To determine the characteristics of blood cell count of patients with HADT, the subjects were asked to fast overnight for 12 hours and their venous blood samples were taken in the morning for full blood count analysis including hemoglobin concentration, red cell count, leukocyte count, neutrophil count, lymphocyte count and platelet count with a hemocyte analyzer (URIT-2900, China).

Vital Signs of Patients with HADT

To explore the characteristics of the vital signs of the HADT patients, the oxygen saturation of the subjects was measured with a pulse oximeter (Ohmeda TuffSat, Palatine, IL, US), and their blood pressure and heart rate were assessed with an electronic sphygmomanometer (OMRON, Tokyo, Japan).

Left Ventricular Function of Patients with HADT

To explore the characteristics of the left ventricular function of the patients with HADT, the left ventricular ejection fraction (LVEF) and fraction shortening (LVFS) of the subjects were also determined with an ultrasound system (SonoSite MicroMaxx, SonoSite Inc., Bothell, WA, USA).

Statistical Analysis

Statistical analysis was performed using the software packages SPSS13.0 version (SPSS Inc., Chicago, IL, USA). Continuous data were given as mean $\pm$ standard deviation (SD). Comparisons of continuous data between two groups were performed by independent-sample *t* test. *p* value less than 0.05 was considered statistically significant.

Table I. Baseline characteristics of HADT patients and healthy individuals.

Characteristics	Control group (n = 31)	HADT group (n = 117)	p value
Age (year)	19.32 ± 1.11	21.52 ± 2.74	0.000
Height (cm)	171.84 ± 5.56	172.32 ± 5.11	0.65
Weight (kg)	64.29 ± 7.53	61.36 ± 6.96	0.04
BMI (kg/m ²)	21.78 ± 2.45	20.65 ± 2.04	0.009

Results

Baseline Characteristics

Baseline characteristics of the study population were summarized in Table I. Data were presented as mean ± SD. All participants were divided into two groups: HADT group and healthy control group. There was no significant difference between the two groups in terms of height. However, compared with those in control group, weight and BMI were lower ($p < 0.05$), but age was higher ($p < 0.01$) in the HADT patient group.

The Prevalence rate of HADT

The prevalence rate of HADT was 66.9% at a high altitude of 4516 m.

Main Symptoms of HADT

The symptoms of HADT were summarized in Table II.

Blood Rheology Indicators

Blood rheology indicators of the study population were summarized in Table III. Our results showed that blood viscosity at different shear rates and hematocrit in the HADT group increased compared with those in control group ($p < 0.01$). Data were presented as mean ± SD.

Full Blood Count Indicators

Full blood count indicators of the subjects were summarized in Table IV. Data were presented as mean ± SD. Compared with those in control group, lymphocyte (LYM) count, neutrophil (NEUT) count, white blood cell (WBC) count

and platelet (PLT) count were lower in the HADT group ($p < 0.01$). However, hemoglobin concentration was higher in the HADT group than that in control group ($p < 0.01$).

Vital Signs

Vital signs of the subjects were summarized in Table V. Data were presented as mean ± SD. Systolic blood pressure (SBP) in the HADT group was lower than that in control group ($p < 0.01$), but no significant difference was found between the two groups in terms of diastolic blood pressure (DBP). Compared with that in control group, heart rate (HR) increased ($p < 0.01$) whereas oxygen saturation (SaO₂) declined ($p < 0.01$) in the HADT group.

Cardiac Function Indicators

Cardiac function indicators of the subjects were summarized in Table VI. Data were present-

Table II. The main symptoms of HADT.

Symptom	Frequency (%)
Hypomnesia	117 (100%)
Hyporosexia	117 (100%)
Cyanosis	117 (100%)
Fatigue	108 (61.7%)
Declined exercise capacity	108 (61.7%)
Anorexia	104 (59.4%)
Weight loss	97 (55.4%)
Gum bleeding	86 (49%)
Palpitate	77 (44%)
Easily catching cold	63 (36%)
Headache	51 (29%)
Skin ecchymosis	46 (26%)

Table III. Blood rheology indicators of HADT patients and healthy people.

Indicators	Control group (n = 31)	HADT group (n = 117)	p value
Blood viscosity (200/s)	6.98 ± 0.64	7.57 ± 0.82	0.000
Blood viscosity (30/s)	8.15 ± 0.69	8.77 ± 0.87	0.000
Blood viscosity (1/s)	15.83 ± 1.07	16.74 ± 1.28	0.000
Hematocrit	0.51 ± 0.04	0.56 ± 0.04	0.000

Table IV. Full blood count indicators of HADT patients and healthy individuals.

Indicators	Control group (n = 31)	HADT group (n = 117)	p value
WBC count (10 ⁹ /L)	5.47 ± 0.95	4.89 ± 1.01	0.005
NEUT count (10 ⁹ /L)	3.17 ± 0.91	2.8 ± 0.83	0.003
LYM count (10 ⁹ /L)	2.29 ± 0.49	2.09 ± 0.47	0.037
Hb (g/l)	182.32 ± 12.17	189.54 ± 12.39	0.004
PLT count (10 ⁹ /L)	162.77 ± 26.6	132.41 ± 39.85	0.004

Table V. Vital signs of HADT patients and healthy individuals.

Indicators	Control group (n = 31)	HADT group (n = 117)	p value
SBP	122.71 ± 10.13	118.15 ± 10.4	0.031
DBP	76.1 ± 8.14	74.26 ± 9.88	0.341
HR (cpm)	76.16 ± 10.36	82.22 ± 11.5	0.009
SaO ₂ (%)	88.1 ± 2.89	86.04 ± 3.22	0.002

Table VI. Cardiac function indicators of HADT patients and healthy individuals.

Indicators	Control group (n = 31)	HADT group (n = 117)	p value
EF (%)	71.29 ± 4.5	68.52 ± 3.87	0.001
FS (%)	40.35 ± 3.58	38.07 ± 3.27	0.001

ed as mean ± SD. Compared with those in control group, both left ventricular ejection fraction ($p < 0.01$) and left ventricular fractional shortening decreased in the HADT group ($p < 0.01$).

Discussion

In the present study, we found that all of the patients with HADT suffered from hypomnesia, hyporosexia and cyanosis, whereas other symptoms such as easily catching cold, headache and skin ecchymosis were not common in these patients.

The body mass index (BMI) is a simple way of measuring one's degree of obesity. BMI categories were nested within broad, generally accepted weight classifications, including underweight (< 18.5), 2 categories of normal weight (18.5-22.4 and 22.5-24.9), 2 categories of overweight (25-27.4 and 27.5-29.9), and 2 categories of obesity (30-32.4 and ≥ 32.5)^{4,5}. In our study, there was no significant difference between the HADT patient group and selected healthy control group in terms of height. However, compared with those in high altitude healthy people, weight

and BMI were lower in HADT patients ($p < 0.05$). The results suggest that HADT patients are thinner than height-matched healthy individuals.

According to our study, 61.7% of HADT patients suffered from fatigue and declined exercise capacity. The blood systolic pressure declined and heart rate elevated in HADT patients compared with those in matched healthy people. Fast heart rate was related to ischaemia and left ventricular function dysfunction⁶. We hypothesized that the occurrence mentioned above symptoms is due to the left ventricular function dysfunction. To prove this hypothesis, we assessed the left ventricular ejection fraction and fractional shortening with M-mode echocardiography. The ejection fraction and fractional shortening are still widely employed for the assessment of left ventricular systolic function and cardiac contractility⁷. Our results showed that EF value and FS value in HADT patients were lower than those in high altitude healthy people. Our results reveal that left ventricular systolic function declines in HADT patients.

In this study, we found that, compared with high altitude healthy individuals, oxygen saturation dropped in HADT patients. This phenome-

non suggests that hypoxemia and tissue hypoxia might lead to the increase of red cell count for adapting hypoxia. Erythrocytosis could cause an increase in blood viscosity and hematocrit⁸. Our results showed, compared with those in high altitude healthy people, hematocrit and blood viscosity at both high shear rate and low shear rate were increased in the HADT patients. These results indicate that blood rheology is abnormal (increased erythrocyte aggregation and reduced erythrocyte deformability) in HADT patients. It is well known that blood viscosity affect microcirculation blood flow. The abnormalities of blood rheology (increased erythrocyte aggregation and reduced erythrocyte deformability) will result in decreased microcirculation blood flow. The microcirculation is a complex system that actively controls the supply of oxygen and nutrients to all tissues. Decreased microcirculation blood flow might directly induce organ dysfunction⁹.

Several studies has demonstrated that high altitude hypoxia exposure had great impact on the generation or function of red blood cells and platelets in the blood. Long-term hypoxia and high altitude exposure could obviously decrease the PLT count. As it is known, platelets play an important role in hemostasis and coagulation. Once PLT count decreases, the risk of bleeding will increase¹⁰. Our results suggest that low PLT count leads to 49% of HADT patients suffering from gum bleeding and 26% of patients suffering from skin ecchymosis.

This study demonstrated that 36% of patients frequently suffered from upper respiratory tract infection (URTI), which might be caused by immune suppression. Immune suppression was, at least in part, responsible for the increased incidence and severity of upper respiratory infections reported at high altitude¹¹. Neutrophils and lymphocytes belong to immune cells. Neutrophils act an important role in non-specific immunity. Lymphocytes play an important role in immune response. Thus, HADT patients suffering from URTI frequently might be caused by a decline in neutrophil and lymphocyte count. Meanwhile, resistance to respiratory infections is mediated by the secretory immunoglobulin A (sIgA), a main effectors of the mucosal immune system. sIgA, which is produced by respiratory mucosa, acting as a first line of defense against colonization of infections agents on mucosal surfaces by neutralization and elimination of viral pathogens^{12,13}.

Therefore, decline of sIgA secretion is associated with suffering from URTI frequently. Our present study showed that WBC count, neutrophil count and lymphocyte count were lower in HADT patients than those in healthy controls. It will be worth to further assess the sIgA secretion in respiratory mucosa of HADT patients.

Conclusions

The prevalence rate of HADT was 66.9% among people moving to a high altitude of 4516 m. HADT is a syndrome of multi-organ dysfunction. It includes impairment of cardiac function, immune depression, microcirculation disturbance and decline of hemostasis and coagulation function. Our present study systematically investigated the clinical characteristics of HADT patients for the first time. These data will contribute to the scientific diagnosis and prevention for HADT patients.

Acknowledgements

This research was supported by the National Basic Research Program of China (973 Program) (2012CB518201), key project of PLA(BWS11J042) and the Special Discipline Program of China(J1310001).

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

- 1) ASKEW EW. Work at high altitude and oxidative stress: antioxidant nutrients. *Toxicol* 2002; 10: 107-119.
- 2) MILLEDGE JS, WEST JB, SCHOENE B. High altitude medicine and physiology. London: Hodder Arnold, 2007.
- 3) WEST JB. English Translation of "Nomenclature, Classification and Diagnostic Criteria of High Altitude Disease in China". *High Alt Med Biol* 2010; 11: 170-171.
- 4) ADAMS KF, LEITZMANN MF, BALLARD-BARBASH R, ALBANES D, HARRIS TB, HOLLENBECK A, KIPNIS V. Body mass and weight change in adults in relation to mortality risk. *Am J Epidemiol* 2013; 179: 135-144.
- 5) ONG T, SAHOTA O, TAN W, MARSHALL L. A United Kingdom perspective on the relationship between body mass index (BMI) and bone healthy:

- A cross sectional analysis of data from the Nottingham Fracture Liaison Service. *Bone* 2014; 59: 207-210.
- 6) FOX K, KOMAJODA M, FORD I. Effect of ivabradine in patients with left-ventricular systolic dysfunction: a pooled analysis of individual patient data from the BEAUTIFUL and SHIFT trials. *Eur Heart J* 2013; 34: 2263-2270.
 - 7) COOLS F, DHUYVETTER D, VANLOMMEL A, JANSSENS S, BORGHYS H, GEYS H, GALLACHER DJ. A translational assessment of preclinical versus clinical tools for the measurement of cardiac contractility: comparison of LVdp/dtmax with echocardiography in telemetry implanted beagle dogs. *J Pharmacol Toxicol Methods* 2014; 69: 17-23.
 - 8) JIANG C, CUI J, LIU F, GUO L, LUO Y, LI P, GUAN L, GAO Y. Mitochondrial DNA 10609T promotes hypoxia-induced increase of intracellular ROS and is a risk factor of high altitude polycythemia. *PLoS One* 2014; 9: e87775.
 - 9) RUIZ C, HERNANDEZ G, ANDRESEN M, INCE C, BRUHN A. Min-report: microcirculatory flow abnormalities in a patient with severe hyperviscosity syndrome. *Clin Hemorheol Micro* 2013; 54: 33-38.
 - 10) NIU Q, ZHANG R, ZHAOM, ZENG S, HUANG X, JIANG H, AN Y, ZHANG L. Differences in platelet indices between healthy Han population and Tibetans in China. *PLoS One* 2013; 8: e67203.
 - 11) OLIVER SJ, MACDONALD JH, HARPER SMITH AD, LAWLEY JS, GALLAGHER CA, DI FELICE U, WALSH NP. High altitude impairs in vivo immunity in humans. *High Alt Med Biol* 2013; 14: 144-149.
 - 12) TIOLLIER E, GOMEZ-MERINO D, BURNAT P, JOUANIN JC, BOURRILHON C, FILAIRE E, GUEZENNEC CY, CHENNAOUI M. Intense training: mucosal immunity and incidence of respiratory infections. *Eur J Appl Physiol* 2005; 93: 421-428.
 - 13) GLEESON M, PYNE DB. Exercise effects on mucosal immunity. *Immunol Cell Biol* 2000; 78: 536-544.