WILDERNESS & ENVIRONMENTAL MEDICINE, **26,** 124–132 (2015)

ORIGINAL RESEARCH

Positive Association of D Allele of ACE Gene With High Altitude Pulmonary Edema in Indian Population

Shuchi Bhagi, MPhil; Swati Srivastava, PhD; Arvind Tomar, MSc; Shashi Bala Singh, PhD; Soma Sarkar, PhD

From the Defence Institute of Physiology and Allied Sciences, Defence Research and Development Organization, Delhi, India (Ms Bhagi, Drs Srivastava, Singh, and Sarkar); and the Defence Research and Development Establishment, Defence Research and Development Organization, Gwalior, India (Mr Tomar).

Objective.—High altitude pulmonary edema (HAPE) is a potentially fatal high altitude illness occurring as a result of hypobaric hypoxia with an unknown underlying genetic mechanism. Recent studies have shown a possible association between HAPE and polymorphisms in genes of the renin-angiotensin-aldosterone system (RAAS), which play a key role in sensitivity of an individual toward HAPE.

Methods.—For the present investigation, study groups consisted of HAPE patients (HAPE) and acclimatized control subjects (rCON). Four single-nucleotide polymorphisms (SNPs) were genotyped using restriction fragment length polymorphism (RFLP) analysis in genes of the RAAS pathway, specifically, renin (*REN*) C(–4063)T (rs41317140) and *REN*$^{i8-83}$ (rs2368564), angiotensin (*AGT*) M (235)T (rs699), and angiotensin-converting enzyme (ACE) insertion/deletion (I/D) (rs1799752).

Results.—Only the I/D polymorphism of the ACE gene showed a significant difference between the HAPE and rCON groups. The frequency of the D allele was found to be significantly higher in the HAPE group. Arterial oxygen saturation levels were significantly lower in the HAPE group compared with the rCON group and also decreased in the I/D and D/D genotypes compared with the I/I genotype in these groups. The other polymorphisms occurring in the *REN* and *AGT* genes were not significantly different between the 2 groups.

Conclusions.—These findings demonstrate a possible association of the I/D polymorphism of the ACE gene with the development of HAPE, with D/D being the at-risk genotype.

Key words: HAPE, RAAS, polymorphism, arterial oxygen saturation, ACE gene

Introduction

High altitude illness may be divided into different syndromes that affect lowland or highland residents ascending to altitudes greater than those to which they are accustomed. Susceptibility to high altitude maladies is considered as the major factor limiting the individual's performance at high altitude (HA). The processes of acclimatization help in maintenance of physical performance in tolerant individuals, whereas the nonacclimatized maladapted individuals succumb to life-threatening complications. These HA syndromes most commonly include acute mountain sickness, high altitude pulmonary edema (HAPE), and high altitude cerebral edema. Development of HAPE is a potentially fatal condition affecting healthy lowlanders or nonacclimatized individuals. This disease is a form of noncardiogenic pulmonary edema that originates with accelerated permeability and usually occurs within 2 to 4 days of ascent above 2500 to 3000 m.[1–3] Its initial pathogenesis is owing to nonuniform hypoxic pulmonary vasoconstriction leading to pulmonary capillary stress failure and a high-permeability type of edema of the lungs in the absence of infection with normal left atrial pressure.[4] Acclimatization at HA is mediated by a combination of mechanisms involved in sustained oxygen delivery, involving increase in ventilation, cardiac output, and hemoglobin concentration, as well as metabolic changes.[5] Genetic polymorphisms in many genes play a pivotal role in determining susceptibility of an individual to HAPE.[6]

Conflict of interest: The authors declare that they have no conflict of interest.

Corresponding author: Swati Srivastava, PhD, Defence Institute of Physiology and Allied Sciences, Lucknow Road, Timarpur, Delhi 110054, India (e-mail: sri_swati@rediffmail.com).

It is well known that the renin-angiotensin-aldosterone system (RAAS) acts as a circulating hormonal system that regulates blood pressure, electrolyte balance, and fluid homeostasis.[7] Genetic variations occurring in the genes of the RAAS pathway have been studied in various populations with conflicting results in relation to hypertension,[8] diabetic complications,[9] coronary heart disease,[10] and renal disease.[11] Many studies have suggested the role of human RAAS in HA hypoxic adaptation also.[12] RAAS is an enzymatic cascade that is composed of renin (REN), which converts angiotensinogen (AGT) to angiotensin, which is in turn cleaved by angiotensin-converting enzyme (ACE) to produce angiotensin II (AngII), the final product of this pathway. AngII in turn interacts with its receptors to release aldosterone and bring about its other biological actions. Renin plays a crucial role in regulation of blood pressure, and its polymorphisms have been shown to have both positive[13] and negative[14] associations with essential hypertension. The *AGT* gene variants have also been studied in relation to hypertension[15] and diabetes[16] with conflicting results. Woods et al[17] suggested the preferential association of the I allele of ACE in the maintenance of arterial oxygen saturation (Sao_2) at HA.[17] The ACE gene is also shown to be involved in blood pressure regulation.[18] Interindividual variability of plasma ACE levels is determined by the polymorphic variant of ACE[19]: the I allele for lower ACE activity and the D allele for elevated ACE activity.[19,20] Rapidly ascending climbers with an I/I genotype were shown to maintain a higher Sao_2 at rest and during exercise at HA.[17] An excess frequency of the I allele has been reported in elite mountaineers,[12] recreational climbers,[21] and HA adaptation.[22] Hypoxia-induced rise in minute ventilation was also greater in those with an ACE I/I genotype than a D/D genotype.[23]

In view of the above literature, the present study was undertaken to determine the possible association of 4 genetic variants (single-nucleotide polymorphisms [SNPs] and insertion/deletion [I/D] polymorphism) of 3 genes of the RAAS pathway, ie, *REN* C(-4063)T (rs 41317140)) and A/G$^{i8\text{-}83}$ (rs 2368564), *AGT* M(235)T (rs 699), and ACE (I/D) (rs 1799752) with HAPE in the Indian population and also to examine the association of these polymorphisms with Sao_2 levels.

Methods

SUBJECTS

A total of 154 Indian lowlanders, unrelated to each other to the best of our knowledge, belonging to the Indian Army were studied. These subjects were serving Army personnel and had no familial relationships among them. They were acutely introduced to HA ($\geq$3500 m) in Leh, in the Ladakh region of India, at different times (over the course of approximately 2 years) and were heterogeneous without predominance of any particular ethnic group. Because these subjects were all healthy Army personnel, they did not have any medical history of other pulmonary disorders. They were born and recruited at sea level and introduced to HA on posting; of these, 75 of the volunteers were acclimatized controls (rCON) and 79 individuals were those with high altitude pulmonary edema (HAPE), which had developed within 48 to 72 hours after ascent to HA. HAPE was diagnosed by physicians through chest radiography and other clinical parameters. The study was approved by the Institutional Ethics Committee of the Defence Institute of Physiology and Allied Sciences (DIPAS), and written informed consent was obtained from the volunteers before recruiting them for study. Approximately 5 mL of venous blood was collected in K_3 EDTA vacutainers (Greiner GmbH, Pleidelsheim, Germany), stored at 4°C, dispatched on ice to the Delhi laboratory, and stored at –20°C until further processing.

PHYSIOLOGICAL MEASUREMENTS

Physiological recordings and sample collection for 154 subjects (79 HAPE and 75 rCON), such as age, body weight, heart rate (HR), blood pressure, and Sao_2, were measured at HA (Table 1). Measurements of Sao_2 and HR were performed in the seated volunteers by finger pulse oximeter (Nellcor N-20P, Covidien, Dublin, Ireland, and MD-300, Vandagraph Ltd, Keighley, UK) on warm hands. During recording, the volunteers breathed room air, and their Sao_2 values were recorded after they remained constant for at least 1 minute (Figure 1). The volunteers were not on medication. The Sao_2 in HAPE individuals was measured immediately on admission to the hospital before the start of medication and oxygen supplementation.

GENOMIC DNA ISOLATION AND GENOTYPIC ANALYSIS

Blood samples were taken from –20ºC storage and thawed on ice. Extraction of genomic DNA from peripheral leukocytes was performed using phenol extraction from sodium dodecyl sulfate–lysed, proteinase K–treated cells by overnight incubation at 37°C. A quantitative check of DNA was done using DNA/RNA Quant calculator (Amersham Pharmacia, Amersham, UK). For qualitative check, DNA samples were diluted to concentration of 20 ng/μL and loaded on 0.7% agarose gel containing ethidium bromide (EtBr) and run in 0.5× Tris/borate/EDTA buffer for approximately 15 minutes. Gel images were visualized under UV light in a Fluor-S Multi-Imager with Quantity One software (BioRad, Hercules, CA). The present study evaluated 4 genotypic polymorphisms in genes of the RAAS pathway selected in view of their functional relevance in the

Download English Version:

https://daneshyari.com/en/article/2613430

Download Persian Version:

https://daneshyari.com/article/2613430

Daneshyari.com