Journal of Cardiology & Diagnostics Research
JCDR, 1(1): 13-18
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Original Review: Open Access

Why do not all people Ill with High-Altitude Pulmonary Edema?

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Received April 26, 2018; Accepted May 24, 2018; Published August 25, 2018

ABSTRACT

High-altitude pulmonary edema (HAPE) occurs in unacclimatized individuals who are rapidly exposed to altitude in excess of 2500 m above sea level. A working hypothesis of the etiology of HAPE suggests that hypoxic pulmonary vasoconstriction is extensive and precapillary resistance is elevated. The result is dilatation of the capillaries and capillary injury, with leakage of protein and red cells into the alveoli and airways. However, the question remains: why HAPE develops only in some individuals, who are rapidly exposed to high-altitudes? Our experience in studying the genetics of human adaptation to high-altitude shows that the hereditary factor may plays a role. Based on study of chromosomal heterochromatic regions (HRs) the hypothesis of thermoregulation at the cell level has been advanced. The essence of the cell thermoregulation is elimination of the temperature difference between the nucleus and cytoplasm. It has been shown that the amount of HRs influence on the level of the human body heat conductivity. The amount of chromosomal HRs is subject to wide variability in human population. When individuals with a high amount of HRs happened to be in cool high-altitude condition their bodies are rapidly and deeply cooled due to their high body heat conductivity with all the ensuing consequences. Therefore, it is possible that under all other conditions being equal, HAPE most often develops in individuals with a large amount of chromosomal HRs in the genome.

Keywords: High-Altitude Pulmonary Edema, Q-Heterochromatin, Condensed Chromatin, Human Body Heat Conductivity, Human Adaptation

INTRODUCTION

High-altitude pulmonary edema (HAPE) occurs in unacclimatized individuals who are rapidly exposed to altitude in excess of 2450 m. It is commonly seen in climbers and skiers who ascend to high altitude without previous acclimatization. Initial symptoms of dyspnea, cough, weakness, and chest tightness appear, usually within 1-3 days after arrival. Common physical signs are tachypnea, tachycardia, rales, and cyanosis. Descent to a lower altitude, nifedipine, and oxygen administration result in rapid clinical improvement. HAPE represents one of the few varieties of pulmonary edema where left ventricular filling pressure is normal (Hultgren, 1996).

The majority of persons who ascend rapidly to terrestrial elevation higher than approximately 2500 m undergo an unpleasant period of acclimatization. During this time, they have a variety of symptoms, the most prominent of which are headache, nausea, vomiting, and insomnia that are collectively referred to as acute mountain sickness (Hall et al., 1965; Singh et al., 1969; Hackett, 1980). Acute mountain sickness is part of a continuum of diseases related to ascension to high altitudes (Houston, 1976) that includes the infrequent life-threatening conditions high-altitude pulmonary edema (Schoene, 1985) and cerebral edema (Hamilton et al., 1986).

The pathophysiological mechanisms of HAPE have been studied fairly well. Physiologic studies during the acute stage have revealed a normal pulmonary artery wedge pressure, marked elevation of pulmonary artery pressure, severe arterial unsaturation, and usually a low cardiac output. Pulmonary arteriolar (precapillary) resistance is elevated. A working hypothesis of the etiology of HAPE suggests that hypoxic pulmonary vasoconstriction is extensive but not uniform. The result is over perfusion of the remaining patent vessels with transmission of the high pulmonary artery pressure to capillaries. Dilatation of the capillaries and high flow results in capillary injury, with leakage of protein and red cells into the alveoli and airways (Hultgren, 1996).

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Citation: Ibraimov I A. (2018) Why Do Not all people Ill with High-Altitude Pulmonary Edema? J Cardiol Diagn Res, 1(1): 13-18.

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However, the question remains: why HAPE develops only in some individuals, who are rapidly exposed to altitudes in excess of 2500 m above sea level? For example, HAPE was originally thought to be rare in women, but subsequent studies have shown that women do develop HAPE, albeit at a lower incidence than men. A review of 229 cases of HAPE revealed a male preponderance of 87% (Lobenhoffer et al., 1982; Sophocles, 1986; Hochstrasser et al., 1986; Hultgren et al., 1996). Although HAPE is more frequent in males, no sex difference has been noted in acute mountain sickness (Hackett et al., 1976). Children are more susceptible to HAPE than adults. A study made in Peru of 1157 ascents from see level to 3782 m reported that individuals aged 13-20 years had the highest incidence of HAPE (17%), whereas adults age 21 or older had an incidence of only 3% (Hultgren and Marticorena, 1978). Our long-term experience in studying the genetic basis of human adaptation to some extreme climatic and geographic conditions, including the high mountains of the Pamir and the Tien Shan, shows that the hereditary factor may plays a role in the development of HAPE.

METHODS AND RESULTS

Sample Characteristics

During the last 50 years, scientists of our Center have systematically studied the physiology, pathology and genetics of the inhabitants of the highland areas of the Pamir and Tien Shan. During these years we managed to observe only one case of HAPE that occurred with one of our colleagues in the Eastern Pamir in the village of Murgab located at an altitude of 3600 m above sea level (asl). We left by car from the city of Osh (160 m asl) and reached the village in two days, driving through, among other things, the three highest mountain passes (from 3,615 to 4,655 m asl) of the Pamirs. The trip itself was carried out by the members of the scientific expedition relatively well and placed in a local hotel. However, at midnight, the condition of one of the expedition members (male, 24 years old, physically healthy) began to deteriorate sharply. Expedition doctors diagnosed HAPE, conducted all necessary medical interventions and the next day in the morning they flown down to Osh city for further observation. Everything ended well, after the landing in the airport he felt normal and soon he went to see the sights of the city.

Cytogenetic Methods

Chromosomal preparations were made using short-term cultures of peripheral blood lymphocytes, with the exception of newborn infants where umbilical blood was used. The cell cultures were processed according to slightly modified (Ibraimov, 1983) conventional methods (Hungerford, 1965). The dye used was quinacrine mustard. All the chromosomal preparations were analyzed by one and the same cytogeneticist (A.I.I.) to investigate chromosomal Q-HR variability. Calculation and registration of chromosomal Q-HRs was performed using the criteria and methods described in detail elsewhere (Ibraimov et al., 1982, 1990).

Quantitative Characteristics of chromosomal Q-HR Variability

Q-HR variability of autosomes in populations is usually described in the form of three main quantitative characteristics: 1) The distribution of the number of Q-HRs in a population, i.e., distribution of individuals having different numbers of Q-HRs in the karyotype regardless of their location on seven Q-polymorphic autosomes, which also reflected the range of Q-HRs variability in the population genome; 2) The derivative of this distribution, an important population characteristic, is the mean number of Q-HRs per individual; 3) The frequency of Q-HRs on seven Q-polymorphic autosomes (3, 4, 13-15, 21 and 22) in the population. Despite the fact that in human autosomes there are twelve loci in which Q-HRs can be detected (3 cen, 4 cen, 13 p11, 13 p13, 14 p11, 14 p13, 15 p11, 15 p13, 21 p11, 21 p13, 22 p11, 22 p13), individuals with 24 Q-HRs in their genome could exist, but such cases have not as yet been reported. In individuals of a population the number of Q-HRs on the autosomes usually ranges from zero to ten (Yamada & Hasegawa, 1978; Al-Nassar et al., 1981; Ibraimov & Mirrakhimov, 1985).

Results and Discussion

After returning to the Center, in all members of the expedition examined their karyotype, including the polymorphism of chromosomal Q-HRs. It turned out that they are not different from normal individuals in terms of the location, number, size and intensity of fluorescence of chromosomal Q-HRs. The only difference was in the individual who endured HAPE: he has a large amount of chromosomal Q-HRs in his karyotype. As can be seen from Fig. 1 in this individual on three autosomes (3, 13 and 21) and on the Y chromosome, there are seven chromosomal Q-HRs different sizes and fluorescent intensities.

The fact is that in Kyrgyzstan, the number of chromosomal Q-HRs in individuals in the population ranges from 0 to 7, averaging 2.8 (Ibraimov et al., 1982; 1986). But in order to clarify our position on the possible role of heredity in the pathogenesis of HAPE, it is necessary to have some idea of the nature of chromosomal polymorphism, based on variability, the so-called heterochromatic regions of chromosomes.

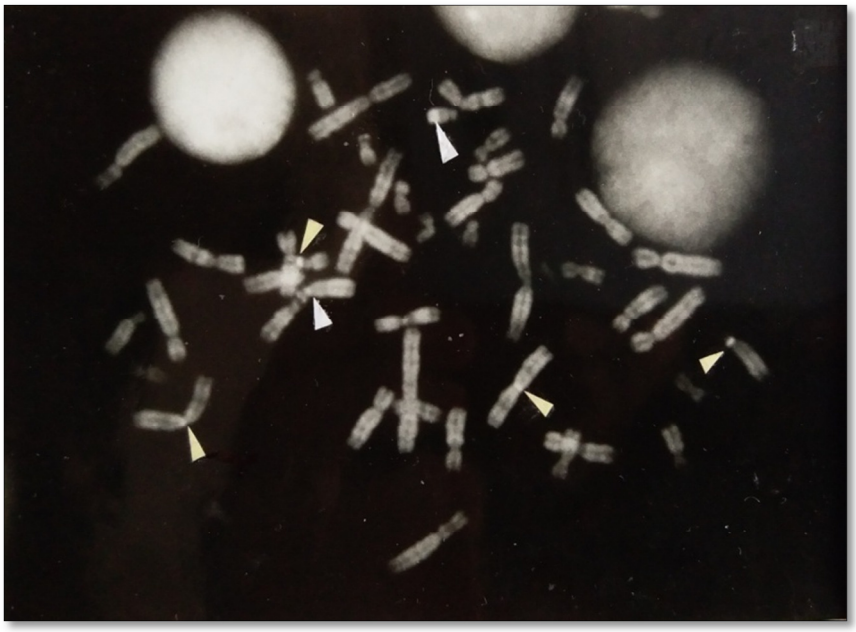

Figure 1. Q-heterochromatin regions localized on the Q-polymorphic loci of three autosomes (3cen; 3cen; 13p11; 13p11; 13p13; 21p13) and on q12 locus of chromosome Y.

To-date two types of heterochromatin are recognized: Q- and C-heterochromatin (Caspersson et al., 1970; Arrighi & Hsu, 1971; Paris Conference, 1971; Suppl., 1975). Despite the fact that chromosomal C- and Q-heterochromatin are defined by a single term, "constitutive heterochromatin", they are undoubtedly significantly different intrachromosomal structures (Prokofyeva-Belgovskaya, 1986). There are several significant differences between them: C-heterochromatin is found in the chromosomes of all the higher eukaryotes, while Q-heterochromatin - only in man (*Homo sapiens*), the chimpanzee (*Pan troglodytes*) and gorilla (*Gorilla gorilla*) (Pearson, 1973, 1977). C-heterochromatin regions (C-HRs) are known to be invariably present in all the chromosomes of man, varying mainly in size and location (inversion). However, chromosomal Q-HRs is subject to considerably greater variability in human populations as compared to C-HRs (Erdtmann, 1982).

Regarding the distribution pattern of chromosomal Q-HRs at the population level the following reliable data obtained: 1) Q-HRs are found on certain loci of only seven autosomes in both sexes, as well as on the Y chromosome in males; 2) despite the fact that in the human karyotype there are 25 loci where chromosomal Q-HRs could potentially be found, in reality the maximal number of Q-HRs does not exceed 10; 3) in human populations the number of Q-HRs in the karyotype usually ranges from 0 to 10; 4) the amount of Q-HRs in the population genome is best determined by the value of the mean number of Q-HRs per individual ($\bar{x}$); 5) there are significant interpopulation differences in the quantitative content of chromosomal Q-HRs in the population genome. These differences proved to be related to features of the ecological environment of the place of permanent residence and not to the racial and ethnic composition of the populations. Changes in the amount of Q-HRs in the population genome have a tendency towards a decrease from southern geographical latitudes to northern ones, and from low-altitude latitudes to high-altitude ones **(Fig. 2)**;

Figure 2. The mean number of Q-HRs per individual in the native populations of Eurasia and Africa (Reproduced from Ibraimov, 2003, with permission of the publisher): a = Chukchi of Chukotsk (n = 132); b = Yakuts of Yakut ASSR (n = 127); c = Selkups of eastern Siberia (n = 90); d = Nenets of eastern Siberia (n = 117); e = Khants of eastern Siberia (n = 54); f = Mongolians of the MPR (n = 72); g = Chinese of northern China (n = 124); h = Kazakhs of southern Kazakhstan (n = 101); i = Kirghiz of Pamir and Tien Shan (n = 603); k = Russians of Bishkek (n = 200); l = Ethiopians of Ethiopian uplands (n = 52); m = Guinea-Bissau Negroes (n = 13); n = Mozambique Negroes (n = 148); o = Zimbabwe Negroes (n = 34); p = Angola Negroes (n = 132); q = Indians of northern India (n = 58).

6) in different age groups $\bar{x}$ values differ, the greatest number of Q-HRs is characteristic of newborns, while the least number - in elderly subjects; 7) individuals that are capable to adapt to the extreme climate of high altitudes (e.g. mountaineers) and to that of the Far North (e.g. borers - oil industry workers of the Jamal peninsula, Eastern Siberia) have extremely low numbers of Q-HRs in their genome (Geraedts and Pearson, 1974; McKenzie and Lubs, 1975; Buckton et al., 1976; Lubs et al., 1977; Yamada and Hasegawa, 1978; Al-Nassar et al., 1981; Stanyon et al., 1981; Ibraimov and Mirrakhimov, 1982a,b,c, 1985; Ibraimov et al., 1982; 1986; 1990; 1991; 2013; Kalz et al., 2005; Décsey et al., 2006)**.**

Some physiological effects of the amount of chromosomal HRs in the genome on the human body are also known. Based on study of distribution of chromosomal HRs in various human populations, in norm and at some forms of pathology the hypothesis about thermoregulation existence at the cell level has been presented. The essence of hypothesis of cell thermoregulation (CT) is elimination of the temperature difference between the nucleus and cytoplasm when the nucleus temperature becomes higher than the cytoplasm temperature (Ibraimov, 2003). The condensed chromatin (CC) localized between a nucleus and cytoplasm is made of different types of chromosomal HRs. For this reason, CC is subject to wide variability in population. Obviously, the density of the CC packing depends on the quantity of chromosomal Q-HRs in its structure that can affect upon its heat-conducting ability.

It has been experimentally shown that the effect of CT can be indirectly assessed by the level of the body heat conductivity (BHC). In particular, we were able to show that individuals in a population significantly differ from each other in terms of BHC level. In other words, there are some parallels in the distribution of the amount of chromosomal Q-HRs and variability of BHC at the level of human populations (Ibraimov et al., 2014).

As is known, with HAPE, dilatation of the capillaries and high flow results in capillary injury, with leakage of protein and red cells into the alveoli and airways. A working hypothesis of the etiology of HAPE suggests that hypoxic pulmonary vasoconstriction is extensive (see above). We believe that the cause of pulmonary vasoconstriction in addition to hypoxia, perhaps, is the cold inherent in the high-mountain climate. Since the individuals in the population differ in the level of the BHC, there is nothing unexpected in the assumption that the HAPE will most often be exposed to individuals whose bodies are rapidly and deeply cooled due to their high heat conductivity. Moreover, in individuals with a high BHC during rapid cooling of the body in the alveoli and airways, in addition to protein and red cells, condensates of water can form (effusion). To this condition can contribute the tachypnea, caused by the struggle for oxygen. Such individuals, in our understanding, are just those whose BHC is very high due to the fact that there are a lot of chromosomal Q-HRs in their genome that determine the density of the CC (Ibraimov, 2003, 2017a, Ibraimov et al., 2014).

Of course, we are aware that on the basis of only one observation one cannot make such an unambiguous and promising conclusion. As an excuse, we can only note that: a) in itself, HAPE is not a frequent phenomenon in high mountain medicine; b) for almost 40 years of our Center, we have not been able to examine an individual whose HAPE diagnosis was diagnosed by highly qualified specialists; c) no one in the world has studied the karyotype of individuals who have endured HAPE to the subject of chromosomal Q-HRs polymorphism. However, it would be interesting if anyone looked at the karyotype of individuals who had endured HAPE and calculated the number of chromosomal Q-HRs under a fluorescent microscope.

A question may arise: is there any evidence that chromosomal Q-HRs are related to human pathology. Our experience shows that chromosomal Q-HRs have to do with at least some purely human forms of pathology, like atherosclerosis, obesity, drug addiction and alcoholism (Ibraimov, 2016b, c, 2017a,b). Moreover, there is reason to believe that only a man and two higher primates (chimpanzees and gorilla) suffer from common cold because of the presence of chromosomal Q-HRs in their genome in addition to C-HRs (Ibraimov, 2016a). The fact is that Q-heterochromatin is present in the genome only in man, the chimpanzee and gorilla (see above).

Finally, there is one more important circumstance, to date, no satisfactory animal model of HAPE has been developed. This may indicate that, perhaps, HAPE is another form of purely human pathology. The reason for this can be a high variability in the number of chromosomal Q-HRs in the genome of human populations, the consequence of which is the existence of individuals with different levels of BHC with all the ensuing consequences.

So, how do we explain why not all people ill with HAPE? The following assumption seems highly probable to us. Among the animals studied, only three species of higher primates have both types of constitutive heterochromatin – C and Q-HRs. Therefore, they must have the highest level of BHC. However, unlike chimpanzees and gorillas, the genome of human populations is characterized by a wide quantitative variability of chromosomal Q-HRs. Therefore, it is possible that under all other conditions being equal, HAPE most often develops in individuals with a large amount of chromosomal Q-HRs in the genome.

ACKNOWLEDGMENTS

I apologize to those authors whose work is not cited or only cited through reviews. The reason for this is only the space limitations.

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