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CHRONIC MOUNTAIN SICKNESS: THE REACTION OF PHYSICAL DISORDERS TO CHRONIC HYPOXIA

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Chronic mountain sickness (CMS) is a condition in which hematocrit is increased above the normal level in residents at high altitude. In this article we take issue with the 'Consensus Statement On Chronic And Subacute High Altitude Diseases" of 2005 on two essential points: using a questionnaire to evaluate the symptoms of CMS to use the term "loss of adaptation" as opposed to "adaptation to disease in the hypoxic environment". We opine that CMS is rather an adaptive reaction to an underlying malfunction of some organs and no specific symptoms could be quantified. To substantiate our line of reasoning we reviewed 240 CMS cases seen at the High Altitude Pathology Institute in La Paz. Patients who had a high hematocrit (>58%) underwent pulmonary function studies in search for the cause of hypoxia: hypoventilation, diffusion alteration, shunts, and uneven ventilation-perfusion. The tests included arterial blood gas tests, chest x-rays, spirometry, hyperoxic tests, flow-volume curves, ventilation studies at rest and during exercise, ECG, exercise testing and doppler color echocardiography to assess heart structure and function. When correlated with clinical history these results revealed that CMS is practically always secondary to some type of anomaly in cardio-respiratory or renal function. Therefore, a questionnaire that tries to catalog symptoms common to many types of diseases that lead to hypoxia is flawed because it leads to incomplete diagnosis and inappropriate treatment. CMS, once again, was shown to be an adaptation of the blood transport system to a deficient organs' function due to diverse disease processes; the adaptation aimed at sustaining normoxia at the cellular level in the hypoxic environment at high altitude.

Key words: *altitude, chronic mountain sickness, erythrocythemia, hypoxia*

INTRODUCTION

The 'Consensus statement on chronic and subacute high altitude diseases' was published in 2005 (1). Can normal ranges of medical variables at sea level

be applied to high altitudes residents? Although the answer seems obvious, the implications of such a question need to be fully understood. Blood-doping is a controversial issue in all sports, because the understanding of a high hematocrit is far from complete (2). Whereas the sea level physician considers the hematocrit of high altitude residents as increased (by sea level standards), the high altitude physician interprets this as normal for the population. In the case of chronic mountain sickness (CMS), where hematocrit is above that of the normal population, the sea level physician classifies it as increased polycythemia, while at high altitude it is simply called polycythemia. This is the theory of relativity applied to high altitude medicine.

Polycythemia is characteristically present in patients 40 years or older with hypoventilation, low arterial oxygen tension, low oxyhemoglobin saturation, and cyanosis, with or without CO_2 retention. The hematocrit or packed red cell volume (PCV) can be determined by centrifugation or more recently electrochemically. Polyerythrocythemia has to be differentially diagnosed between absolute (stable condition) that refers to the true hematocrit and relative (acute loss of balance) where it is due to dehydration secondary to perspiration, hyperventilation, or altered diuresis with a temporary decrease of plasma volume. The latter is of short duration if the negative factor disappears.

When normal animals or human beings ascend to high altitude the hemodynamic and pneumodynamic pumps play the fundamental role in the acute stage of adaptation to hypoxia (*Fig. 1*). During chronic residence in hypoxic environments, these two pumps receive some relief through the increase of hemoglobin, oxygen content, and associated mechanisms making oxygen transport to the tissues as efficient as that at sea level. Cellular function is 100% effective in a well adapted resident of high altitude.

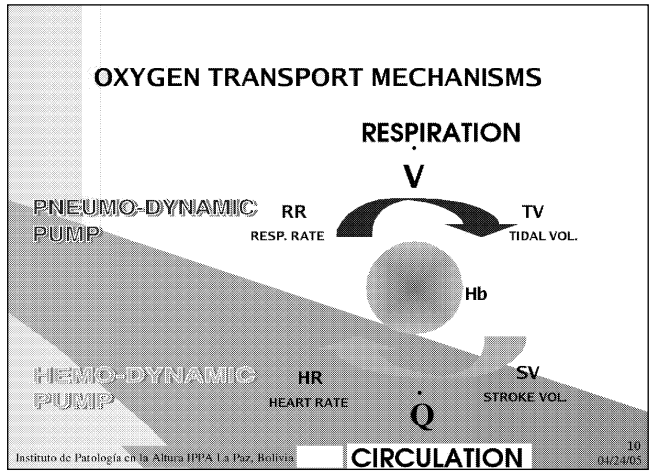

Fig. 1. The pneumo-dynamic and hemo-dynamic pumps and the hemoglobin molecule in the joint role for oxygen transport to tissues.

CMS can be found at altitudes above 2000 m. However polyerythrocythemia also exists at sea level in patients with severe pulmonary disease who require supplementary oxygen. There is, of course, an altitude at which everyone would get CMS, if it is only considered to be an increase of the hematocrit. When the respiratory frequency and ventilatory capacity are unable to compensate the extreme hypoxia, the last resort for the human being is to develop severe pulmonary hypertension (right heart hypertrophy) and to increase the number of the red cells. All permanent residents will be sick with CMS at 5500 m. Should this be called sickness or normal adaptation? For example, at the mine of Chorolque (5562 m) in Bolivia, not everyone has an equal capacity of adaptation. Thus CMS will be more severe in some, and they will nevertheless survive, a few in miserable conditions.

If one considers that CMS patients are suffering from some type of prior chronic cardiac and/or pulmonary disease, then logically, if they are able to tolerate such low levels of hypoxia in spite of their underlying disease, normal subjects, will also be able to do so, provided they are gradually exposed, and in the environmental case of the mountain, avoid cold exposure. This is how CMS patients, long-term residents of high altitude, having a PaO_2 of around 35mmHg contributed to the idea of extreme tolerance to hypoxia at the altitude of the summit of Mt. Everest, making life possible for humans and animals at any altitude on the surface of planet earth (3, 4).

MATERIAL AND METHODS

The High Altitude Pathology Institute “Clinica IPPA” Database has been reviewed in order to study the incidence of polyerythrocythemia and to analyze the diagnosis of these cases. Of 1823 hemograms performed (excluding repeated tests on the same subject and including only the highest hematocrit found) 240 had a hematocrit above 58%, the threshold level established as normal for 3600m of altitude in the city of La Paz, Bolivia. The data was analyzed using Excel. All patients signed a check-up form prior to their testing and gave their informed consent. They were subject to medical check-ups in order to be diagnosed and receive treatments for their illnesses. Not every case had the same tests performed as the diagnoses were variable.

RESULTS

The mean hematocrit was 64.9% ±6.9(SD), mean age 56.0 ±12.9 years, and mean weight 75.3 ±12.5 kg. The greater CMS incidence was found between 55-60 years of age, 21.1% were females, and 37.2% of the suffered had leucocytosis in the hemogram. There were 32.0% smokers, but no relation was found between the number of cigarettes smoked and polyerythrocythemia. Tachycardia, >100 beats/min, was found in 4% and bradycardia, <60 beats/min, was in 4.3%. No correlation was found between the pulse and polyerythrocythemia. *Table 1* shows the multiple diagnoses found. Only those relevant to cardio-pulmonary and renal

Table 1. Diagnoses of 240 patients that had a hematocrit above 58% at 3510m above sea level.

Diagnosis	%	Diagnosis	%	Diagnosis	%
High blood pressure	27.1	Pulmonary fibrosis	5.0	Cardiac angina	2.1
Nephritis	19.2	Cor pulmonale	4.6	Arterioesclerosis	2.1
Bundle or branch heart blocks	18.3	Asthma	4.6	Pulmonary embolism	2.1
Respiratory or ventilatory insufficiency	16.7	Pulmonary hypertension	4.6	Alveolitis	1.7
Reduced vital capacity	12.9	Bronchitis	4.2	Myocardial infarction	1.7
COPD	8.8	Ventricular arrhythmia	4.2	Uneven ventilation	2.1
Cardiac insuficiency and valve anomalies	7.9	Ventricular hypertrophy	3.3	Bronchiectases	1.3
Pulmonary TB or SilicoTB	7.1	Pulmonary shunts	3.3	Emphysema	1.3
Cardiomegalia	6.7	Hypoventilation	2.9	Sleep apnea	0.8
Phlebitis and thrombophlebitis	5.4	Overweight	2.5	Cerebro-vascular accident	0.8
Chagas or alcohol myocarditis	5.4	Gout	2.5	Atrial fibrillation	0.8

function are included. Most had more than one diagnosis making their condition of a mixed etiopathogenesis.

DISCUSSION

The data presented demonstrate that CMS is secondary to pulmonary and cardiac disease of various etiopathogenesis associated with a low inspired PO_2 in the environment. Likewise, kidney anomalies, nutrition, overweight, and rarely hemoglobin abnormalities, play a role. There are different degrees of this disease in relation to the extent of pulmonary lesions and the individual susceptibility. It affects high altitude natives and all races. Yet these people work, play soccer, develop intellectual activities, and frequently perform better than sedentary normal people.

An experienced observer can accurately diagnose CMS among the crowds, walking through the streets of the bowl-shaped city of La Paz (3100-4100m) and its neighboring city of El Alto “the high plateau” (4100m). Just as well, in Lhasa, Tibet (3500m) where several people in their normal activities can be pinpointed. CMS patients are actually carrying on with their daily life and are not completely incapacitated in their natural environment at high altitude. Periodically, these patients become symptomatic, which forces them to consult a physician. In others, routine blood tests report an increased hematocrit. They sometimes look more cyanotic and have to interrupt their daily activities. All the symptoms are wrongly attributed exclusively to CMS. Under these circumstances many physicians perform phlebotomies, as a therapeutic alternative, a procedure we strongly oppose (5). Still some patients may never carry on with their lives (6).

The city of El Alto (4100m), (where the airport is located) is over 500 meters higher than central La Paz and around 1000m from the bottom of the city. This poses a problem for normal hematocrit values. Physiological changes due to the altitude shifts within the city of La Paz have been reported and are of importance for blood gas interpretation (7). There is an inherent contradiction in setting "normal values" because of the daily altitude changes within the city. People living in El Alto come to consultation at 3510m regularly, which represents changes *in-situ*. Gender differences were studied by analyzing the hemograms from the hematology departments of two hospitals, one situated in La Paz at 3510m and another in the city of El Alto at 4100m. Considering a hematocrit of 56% in adults as the threshold level in La Paz, 28% (of 653) males and 11% (of 1042) females had polyerythrocythemia. In El Alto the figures were much higher: 52% (of 429) males and 26% (of 1070) females.

It is evident from these results that men have a higher incidence of CMS than women at both altitudes, a well known observation (6). In El Alto, there is a higher incidence of cardio-respiratory disease since sanitation and medical assistance is rare due to poverty. Hypoxia *per se* is not the primary cause of polyerythrocythemia, but rather is a trigger. No correlation was found between severe, radiologically evident lung lesions in miners and polyerythrocythemia (8). Females seem to suffer less pulmonary disease, which is the primary cause of CMS. There is a strong suggestion that since the female body is designed by nature to carry out the important role of reproduction, where two individuals, the mother and the child have to use oxygen effectively, the female sex is less prone to polyerythrocythemia. Pulmonary lesions that destroy both the alveoli and capillaries, do not produce shunting. Some people with CMS, who were heavy smokers and later developed lung cancer, gradually became anemic and died of cachexia due to the terminal conditions. The exercise capacity in CMS individuals is obviously reduced. Nevertheless, polyerythrocythemia allows these patients with moderate pulmonary limitation to perform exercise (9, 10). This is highly variable, depending on their exercise habits.

Low SaO_2 is a characteristic of CMS. Breath-holding in normal subjects at high altitude, following a deep inhalation or even just talking during arterial puncture, can alter the PaO_2 significantly, because of the sigmoid form of the oxygen dissociation curve. Hence, SaO_2 fluctuations are both common and confusing for the inexperienced physician (11, 12).

CMS patients, who have been reported to hypoventilate (13), are seen to hyperventilate on oxygen administration (14). Polyerythrocythemia is attributed to pulmonary alterations, such as shunts, diffusion alteration, and ventilation-perfusion inequality, all of which are conducive to a low PaO_2. This, in turn, leads to increased cardio-pulmonary activity that is involved with high oxygen consumption. The organism (as a reflex mechanism) may hypoventilate in order to save "energy" (15). Polyerythrocythemia is a beneficial adaptation mechanism,

which permits CMS patients to hold their breath nearly twice as long as normal (12). Tolerance to extreme hypoxia and hypercapnia also play a role.

Chest X-ray films, CAT scan, or NMR are as mandatory as are the clinical history and the pulmonary function tests in the diagnosis of CMS. In order to study the cause of hypoxemia in CMS, the 4 basic causes (shunt, uneven ventilation, diffusion alteration, and hypoventilation) have to be examined. This is why a sole test of forced vital capacity cannot be conclusive of pulmonary function alteration (16). Furthermore, at high altitude no minimal alterations can be tolerated by some individuals, although they tend to be classified as normal. For example, a small slope in the plateau of the single breath nitrogen washout curve is an alteration that at sea level is insignificant but at high altitude leads to CMS (16).

In general, patients with CMS are examined while attending a regular consultation. Most often, after suffering the disease during many years and perhaps only when they or their family become aware of the change in the color of the skin, particularly in the face. Also, when the consultation is for another kind of disease and the routine laboratory tests report polyerythrocythemia. At this time, the signs and symptoms can be present in different degrees and are prominent or more evident during the triple hypoxia syndrome.

In Monge Medrano's original paper on CMS, he thought that he found polycythemia vera at high altitude (1928). He then realized that it was not exactly the same, so he changed his mind and invented the term "loss of adaptation" which later was complemented with the term CMS (1937 & 1943). The clinical description and observation of an increased hematocrit was an important contribution to high altitude pathology, nearly 80 years ago (17).

Since some scientists affirm that they have found people with CMS without anatomical or functional alterations, the CMS seems to have been a separate kind of pathology. With progressing aging, CMS worsens, which, however, is due to deterioration of the underlying disease. In our experience, for over 50 years, we did not see one case of CMS in otherwise normal individuals, not having other organic disorders. Neither have we seen one case of polycythemia vera at high altitude.

Polycythemia vera is a myeloproliferative disorder of polycythemia accompanied by leukocytosis, increased platelet count, now known as essential thrombocythemia, and can evolve to a very severe hematological disease, which does not happen in CMS. Current research has shown that there is a unique activating mutation in JK2, leaving hardly any doubt about the genetic origin (18, 19). Some authors found that in polycythemia vera, the pulmonary diffusing capacity was greater than in normals (20), being attributed to increased hemoglobin concentrations. Polyerythrocythemia increases the total surface of red blood cells exposed to oxygen, which is another advantage in CMS. However, genetic search for mutations in CMS has been negative by far (21) and this strongly favors our conclusion regarding the pathogenesis of CMS. In terms of genetic predisposition, CMS is most likely to occur in some individuals, over 40 years old, who have a tendency to gain weight. This is due to their predisposition

to respiratory disorders or other diseases that are sensitive to hypoxia. This would include some types of heart, neurological, renal, and hematological diseases.

Gastrointestinal ulcers are frequent findings and can lead to gastro-intestinal bleeding, changing the hematocrit. Several patients with CMS have increased uric acid, and some with evident signs of gout by deposits in the ear helix. Gout can lead to well known pulmonary alterations. Noteworthy is the fact that hypertension is found in 27.1% of the cases analyzed herein. This generally implies kidney disease confirmed by protein loss in the advanced cases. Finger clubbing is present in some, even when they are very young. In broncho-pulmonary lesions of smokers (32% smoked in the observed group), for example, there can be severe cyanosis, low saturation, polyerythrocythemia, and pulmonary hypertension. If they stop smoking, there is significant improvement. This looks the same at sea level, but in chronic hypoxia the patients reach lower oxyhemoglobin saturation levels. Yet another example is some patients with asthma. This illustrates that CMS patients have different etiopathogenesis. At altitude, "cyanotic pulmonary diseases and asymptomatic high altitude polycythemia", as defined by Hultgren (22), are CMS. Moreover, the latter more exactly approaches CMS present at moderate altitude.

We seriously questioned the utility of a scoring system in CMS, since it will only apply to a specific and temporary moment, it is common to many types of disease, and will most probably change within a few days. Also, great differences in scoring will be found, depending on the degree of lung or cardiac function compromise, the type of disease, and of course the altitude. This is because patients who have CMS are subject to viral diseases, bronchitis, colds or even seasonal climate changes (including allergies). We described this as the triple hypoxia syndrome (THS), an acute condition superimposed on CMS (23). The THS is defined as a temporary reduction of the basal low SaO_2 in patients with CMS resulting from three different causes of hypoxia superimposed: high altitude hypoxia, CMS hypoxia, and an acute and reversible hypoxia caused by an acute respiratory infection or cold (24, 25). The third hypoxia is reversible by 24 hours of oxygen administration.

The most appropriate approach to score CMS is the laboratory findings: hemoglobin or hematocrit and oxygen saturation, with or without carbon dioxide retention, depending of the severity of the case. For over 35 years now, we have been using a classification by the number of red blood cells *Table 2* (26), and it has proved to be a good guide in our medical practice for our altitude. The

Table 2. Classification of polyerythrocythemia for 3600 m of altitude. Other altitudes require their own classification.

	RBC (mln/µl)	Hematocrit (%)	Hemoglobin (g%)
Mild	6.5 to 7.5	58.0 to 67.0	19.3 to 22.3
Moderate	7.6 to 8.5	68.0 to 76.0	22.4 to 25.3
Severe	>8.5	>76.0	>25.3

hematocrit of 58% is set as the lower limit of polyerythrocythemia, because patients with lower hematocrit are asymptomatic or in the initial step of developing CMS. These can also be easily reversible. Originally, diagnosis was based on clinical examination, chest x-ray film, and a hemogram. Currently pulse-oximetry provides a fast and simple way of evaluating the oxygen status of these patients. But due to the fact that there are great oscillations in SaO_2 at altitude (11), careful readings have to be taken at rest and with the subject not speaking.

There are no great differences between disease at sea level and at high altitude, in the course of life. We are unaware of life expectancy studies in respiratory disease at high altitude. For example, at sea level in the US, chronic obstructive pulmonary disease (COPD) and emphysema affect 20-30% of the adult population, with more than 60000 deaths/year. The predominant age is over 40 and the predominant sex is male. This is strongly similar to our clinical observations at the La Paz altitude (except the death incidence per year that is not quantified). If patients with CMS have reduced life expectancies, it will be due probably to a reduced life expectancy of chronic lung disease, just as at sea level.

We have followed the patients with CMS for years, into their 80's, but have never made a postmortem. No one has reported, up to date, an autopsy of CMS. Probably, if the pathological alterations were discovered, they would be classified as a cardio-pulmonary disease. Moreover, malnutrition, cor pulmonale, hypercapnia, and a heart rate >100 beats/min are all poor prognostic indicators in COPD at sea level. The same happens at high altitude. Cor pulmonale in patients with CMS is probably an advanced and untreated consequence of respiratory disease. Polyerythrocythemia cannot be absent in many cases.

At sea level, supplementary oxygen has been shown to increase survival. This appears contradictory. It would imply that there is a shorter life expectancy for high altitude residents, but that does not seem to be the case. Ever since the use of penicillin, life expectancy has expanded also at high altitude. Previously, many people died of pneumonia in their forties. With better nutrition, better homes, improved health care, and more hygiene, we are seeing more people live well into their nineties. Perhaps high altitude is the best place to live for some, since the temperatures in La Paz only rarely reach freezing temperatures, the air is dryer, and hence asthma is often greatly improved. When pulmonary insufficiency ensues, a low saturation is present and life can only be sustained by descent to sea level, supplementary oxygen, or polyerythrocythemia. We predict that in the future many cases of polyerythrocythemia will be treated since the hemodynamic pump can be increased through the use of cardiac pacemakers. In cardiac insufficiency with cardiac arrhythmia at high altitude, a pacemaker can significantly reduce the polyerythrocythemia.

Most physicians agree that CMS regresses in around one month on descent to sea level. Patients who re-ascend to high altitude and are exposed to hypoxia again, develop CMS once more. This is a mechanism of adaptation to supply the

necessary oxygen to tissues. The patients from lowlands with chronic pulmonary diseases commonly unnoticed at sea level develop CMS at altitude. Are we going to consider these cases as a loss of adaptation? Certainly not, it is hard to think in such a way.

Lets suppose that 3 individuals, apparently normal, one 20 years old, and two 40 years old, move from the lower part of the city of La Paz at 3000m. They remain for 3 months at 3500m and for another 3 months at 4100m in the city of El Alto. Blood tests will show that the 20 years old and 40 years old have a normal hemoglobin and hematocrit for each altitude. The other 40 years old has increased his hemoglobin to around 20 g%. Can we say that this last one has "lost his adaptation" and that the other two have adapted? The last one has developed chronic mountain sickness. Do we call this "adaptation" or "loss of adaptation"? This is not a hypothesis; it is a fact of common observation. Furthermore, if he has "lost his adaptation", is he unable to live there any longer?

Here, we arrive at the most critical point in health problems. Should this man go to the lowlands, even though he feels well in the prevailing intellectual and physical conditions? When he becomes aware that he has CMS, it becomes a significant economical and social problem. He surely will, from time to time, suffer from colds with headaches, lassitude, sleep disturbance, and so on (as would any healthy subject with a cold). Such symptoms will be diagnosed by physicians as the CMS alteration, but this condition is actually the triple hypoxia syndrome in CMS described above, which is transitory and treatable.

Zubieta-Castillo (Sr) is compelled to explain the importance of the term "adaptation". Any term in medicine implies a concept (knowledge) of the diseases which will set the rules for prevention and treatment (CMS in this case). We include in CMS many kinds of pulmonary disease with chronic hypoxia and feel confident that there is no "loss of adaptation of life at altitude", but rather an adaptation of pulmonary, cardiac, renal or other disease to the hypoxia at high altitude (17). In fact, CMS patients do remarkably well, provided that their basic disease is treated or looked after.

By associating CMS with the term "loss of adaptation", attention has been focused only on the increase in the number of red blood cells. This confusion over terminology has misled many studies. Employing this conceptual framework, many people with pulmonary disorders have been sent to the lowlands in order to reduce their hematocrit, where they have been known to die quite soon. Due to the hot, humid, and oxygen rich environment (an optimum medium for bacteria) there is a worsening of infectious diseases (tuberculosis, and pneumonias for example). Some continue to live as would anyone in the lowlands in any part of the world, with unnoticed mild respiratory or ventilatory impairment.

Another form of treatment was targeted to decrease the hematocrit, by using radioactive compounds, such as phosphorous or cytolytic drugs, such as phenylhidrazine (27). These are totally proscribed by the World Health Organization. Nowadays, the pharmaceutical market is full of "medicines"

announcing that they can "reduce" the number of red blood cells. Phlebotomy has to be renounced, in lieu of the advance of knowledge in hypoxia (5).

Above all, the treatment should address pulmonary alterations, and then cardiac and renal functions have to be restored whenever possible. All prior or accompanying diseases such as hypertension, cardiac insufficiency, pneumonias, flu, and others should be treated accordingly. "*The organic systems of human beings and all other species tend to adapt to any environmental change and circumstance, and never tend towards regression which would inevitably lead to death" (GZC Sr).* We have defined the CMS as follows: "Chronic mountain sickness is present in some high altitude residents with any type of abnormal pulmonary function (increased shunt, impaired diffusion, uneven ventilation, or hypoventilation), sequelae of diverse pulmonary diseases that lead to a sustained low oxygen saturation (in the steep part of the oxygen dissociation curve) and cyanosis, giving rise to pulmonary hypertension and polyerythrocythemia as compensatory mechanisms of adaptation to the disease under hypoxic conditions, being the symptoms and signs reversible by descent to sea level." The understanding of polyerythrocythemia at high altitude is fundamental as it is an endemic disease in ever growing high altitude populations. It is our belief that employing an appropriate conceptual framework in the diagnosis of CMS will lead to better treatment and ultimately to a better quality of life for high altitude populations.

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