Commentary on the consensus statement being prepared for the 6th World Congress on Mountain Medicine, Xining 2004

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Once we have reviewed the various opinions of our colleagues in the Consensus Group on CMS, I am sure that we will improve our knowledge of this disease, which is increasing in importance world wide. In our country CMS is a major concern of public health authorities due to its prevalence in the relatively young and active male population. In addition to thanking all of you, I owe special thanks to Dr. Ge Ri - Li, to Dr. Peter Hackett and to Dr. Fabiola Leon - Velarde for providing all of us with the opportunity to participate in this meeting of the Consensus Group with Dr. Dante Peñaloza. Dr. Peñaloza is truly a pioneer among Peruvian scientists in the understanding of Monge's Disease. His thesis on CMS and the pulmonary circulation, published in 1969, is worth our consideration in the present debate, awakening the interest of us all, although some of us, like me, came to his work late. I thank Fabiola also, for all of her energy in organizing this meeting, and Professor Jack Reeves, a pillar of our organization, whose breadth of knowledge, combined with the simplicity with which he relays his deep understanding of the subject, will guarantee that the summary of the consensus reached will be a comprehensive guide for all us. I also thank Octavio Aparicio, José Farfán, Susan Niermeyer, Stacy Zamudio and Lorna Moore for valuable discussions and editorial assistance.

In concordance with the concepts established in 1998 in Matsumoto, we have done everything possible to use the terms and definitions agreed upon previously. In our hospitals in La Paz, where most cases of CMS are treated, excessive erythrocytosis and hypoxemia are used to define the prevalence of CMS. In some cases, we need better clarification concerning whether the erythrocytosis is secondary to pulmonary or cardiac disease, or whether it is due to respiratory insufficiency secondary to ventilatory mechanical failure or other factors relating to red blood cell or hemoglobin production. (For example, we have found that there are sometimes more than one member of a family with CMS, suggesting the possibility of genetic susceptibility possibility due to abnormalities affecting EPO or some other factor).

We are very interested in the schema presented by Dr, Peñaloza which includes consideration of the level of altitude, ethnic factors, gender and age as based on the experience of our colleagues in China, Kyrgyzia, and the Andes.

The level of altitude is a factor of unquestionable importance. (We suggest that might be better expressed as cumulative years of altitude exposure relative to some given altitude, as is customary in the evaluation of smoking). Among Bolivian Andean peoples, densely populated areas are found between 3 000 and 4 800m. A good example of this is La Paz: our capital city, housing some 1 700 000 persons, ranges in altitude from 3 200 - 4 100m. We find that the prevalence of CMS is greater in persons who live at the higher versus lower range of these altitudes within the city borders. Moreover, thousands of persons are ex-

posed to intermittent hypoxia through the changes in altitude which are experienced daily in relation to work, especially those in certain trades (*e. g.* public transportation) or other reasons.

There is no doubt that young women are protected against CMS; the elegant studies of Dr. Fabiola Leon – Velarde have confirmed prior reports showing that medroxyprogesterone improves ventilation in patients with CMS (Kryger M, 1978, Am. Rev. Resp. Dis – 117). Studies of the underlying hormonal mechanisms influencing ventilatory control and the utility of experimental models to elucidate these mechanisms which potentially contribute to CMS are highlighted by the work of Dr. Lorna Moore, and more recently, Dr. Joseph Vincent in Sprague Dawley rats acclimatized to high altitude. The hematological evaluations we have conducted in La Paz demonstrate the existence of a small number (~0. 5% prevalence) of cases of excessive erythrocytosis in young female students. The clinical course of the disease in these young and otherwise healthy patients is complex, and does not permit a clear classification from an etiological point of view. Needed are other complementary examinations as part of an overall cardiorespiratory evaluation.

In our experience the majority of cases of excessive erythrocytosis in adult, post – menopausal women come from persons living in the highest portion of La Paz (~4100m). These cases should be classified as CMS, since they have all the symptoms of the scoring system. But their CMS appears secondary to respiratory insufficiency likely due, in turn, to obesity, tobacco use, thoracic malformations, etc.

Ethnicity or population ancestry does not seem to have the relevance in our Andean zone that it has acquired in China. While large numbers of Europeans migrated to South America after World War II (and earlier), currently there are fewer such newcomers who settle permanently at high altitude. Partly this is due to downward migration, to lower altitudes within the country that have recently experienced economic growth (e. g. Santa Cruz), or persons moving to other countries. Most persons of European ancestry remaining at high altitudes in Bolivia have intermarried with Andean individuals. Perhaps for this or other reasons (we need more studies), persons of European ancestry do not seem especially prone to developing CMS, unlike the Chinese case where more Han than Tibetans seem to develop the disorder.

With respect to age, we are unable to corroborate the data of Carlos Monge C. and colleagues who find that there is an increase in the prevalence of CMS with age within their Peruvian population. Perhaps the level of altitude to which persons are exposed is a factor contributing to an absence of an age – related increase; we do not have the ability to test large numbers of persons living for extended times at altitudes greater than 4 100m (Beall C et al. Anuario IBBA 1991, 267 – 290) whereas this possibility does exist in Peru. Another factor that has not been sufficiently well defined is nutrition; I note this because we also frequently see anemia secondary to nutritional deficits and its mask cases of CMS leading to an under estimation of its prevalence.

We have found a cases of CMS in young men, whose average age is 20. 4 ±4. 2 years and hemoglobin concentration is 19. 7 ± 1. 5 gm/dL through high school medical examinations. Finding excessive erythrocytosis in young men is both curious and worrisome. It is curious because it runs counter to the expectation that CMS is a condition associated with prolonged duration of altitude exposure or advancing age. It is worrisome because it may indicate that such persons will develop more severe symptoms of CMS at a later age. It is also worrisome because, in the absence of a specific etiology, we cannot at present make specific recommendations for treatment.

Concerning the related discussion of the role of lung disease and smoking, it is quite easy to imagine that these well – known causes of respiratory insufficiency at sea level will have effects that occur earlier and in a more severe form in cities located at high altitude. This is supported by an earlier study in Colorado, indicating nearly a ~40% increase in age – standardized mortality rates from emphysema rates at low (1000 m) to high (3000 m) altitude regions of the state (Moore LG et al., Am Rev Respir Dis 126:225 – 2228, 1982). However, we in La Paz do not find chronic bronchopulmonary obstructive disease as frequently as is the case in cities with a high proportion of tobacco smokers. Likewise, extreme obesity, while not as common in La Paz as in some other cities, is particularly egregious for aggravating hypoxemia. Without question, the prevalence of sub – clinical forms of tuberculosis and occupational exposure to

mining are more common in Bolivia and consequently probably predispose to the development of CMS. Each of these conditions combined with altitude can result in various degrees of secondary erythrocytosis. At extreme altitude (e. g. , Santa Barbara, 4850 m) where hematocrits in excess of 75% are relatively common, side effects such as vascular thromboses require attention as well.

Inclusion of the Pulmonary Arterial Hypertension in the Definition of CMS

After analyzing the information provided by our Chinese – Dr. Wu Tianyi, Dr Ge – Ri Li, the Chinese Association for Altitude Medicine, Kyrgyzian, and Peruvian colleagues, we agree that it is necessary to take pulmonary hypertension into account in the definition of CMS.

But what we have learned in the environment of Bolivia, and especially in La Paz across its range of altitudes, leads me to insist that even more important is the actual level of altitude to which the person is exposed. It is clear that in some cases of CMS of the respiratory type, we observe signs of accentuated pulmonary hypertension, but these cases are much more frequent above 4 100m (Antezana G. 1977, Encuesta cardiovascular en Chorolque 4850). In hospital centers in La Paz, whose average altitude is 3 600m, our reported cases of respiratory type CMS only have mild to moderate elevations in pulmonary artery pressure, and the cases that evolve into a decompensated heart failure are rare. But in trying to achieve uniform criteria and since some such cases occur, we agree with the definition proposed by Dr. Dante Peñaloza, for defining CMS of the respiratory type as being characterized by excessive erythrocytosis, hypoxemia and pulmonary arterial hypertension. Further, according to the level of altitude, cases of CMS – respiratory type may evolve into hypoxic cor pulmonale and, in some cases, to congestive heart failure.

Further study is warranted to determine the natural history of the disease and, more specifically, the time course with which such symptoms occur in relation to the altitude of residence.

Our observations in patients followed at IBBA over 5 or more years, lead us to propose the existence of two clinical pathways for CMS:

1) Respiratory Type CMS, whose dominant signs and symptoms are dyspnea, hypoxemia, cyanosis and mild to moderate pulmonary hypertension which progressively worsen with time.
2) Cardiovascular Type CMS, whose signs and symptoms are more variable and in whom sometimes severe pulmonary hypertension develops.

The respiratory type appears to be the more common form. Its signs and symptoms are identifiable by questionnaire and tests designed to measure respiratory symptoms (*e. g.* , dyspnea, cyanosis). For the cardiovascular type CMS, the signs and symptoms that most frequently appear are unusual fatigue, greater hypoxemia than CMS respiratory type, heart palpitations, irregular heart beats, etc. Specific clinical tests electrocardiographic, radiological, if its possible Holter or Echocardiogram are usefull to confirm de degree of PAH

In conclusion, while I agree that it is important to have a valid, cross – cultural scoring system that permits diagnosis of CMS in much the same way as does the Lake Louise system devised for AMS in the 1990s, I do not think we are yet ready for creating one that is mandatory CMS.

My caution is based on two reasons:

1) To date, only excessive erythrocytosis and hypoxemia are diagnostic in all settings and the appropriate cutoffs for these variables remain debatable.
2) The tests or questionnaires available do not yet permit reliable identification of the more subtle signs and symptoms (e. g. , confusion, headache).

Hopefully, here in the discussion at these meetings, we can make progress toward resolving these two concerns or, at least, determine what will be required to do so. Once such issues regarding the diagnostic criteriafor CMS are resolved, the next key step will be to determine the factors creating differential susceptibility or constitutional vulnerability to this important public health condition.

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