Reviewer's report

Title: Abnormal energy regulation in early life: Childhood gene expression predicts subsequent chronic mountain sickness

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Reviewer: Gustavo R Zubieta-Calleja

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Major Compulsory REvisions

The use of the term “maladaptation syndrome” in reference to Chronic Mountain Sickness in the second sentence of the Abstract is a mistake in our opinion. A serious flaw as this has been part of a subject of discussion in the International Consensus Group in Xining (2), where we had a dissenting point of view. The term “Loss of Adaptation” as originally stated by Carlos Monge in his first descriptions of CMS over 80 years ago was, after long and difficult discussions, dropped from the statement.

“The organic systems of human beings and all other species tend to adapt to any environmental change and circumstance within an optimal period of time, and never tend towards regression which would inevitably lead to death” (1)

We stated our concepts in regards to CMS within the aforementioned group (comments are available, on-line at http://www.geocities.com/CapeCanaveral/6280/cmsdisc.html).

Consequently, there is too much speculation about CMS, yet not clearly defined as a unique individual entity but rather due to multiple diseases. Polycythemia (increase of red blood cells above normal values, previously known as excessive erythrocytosis, increased polycythemia, erythremia) is a sign that arises from diverse pulmonary, cardiac, renal, hematological, neurological alterations that at high altitude phenotypically expose the disease. This fundamentally due to the steep portion of the oxygen dissociation curve.

It is well known that genetics pre-dispose to specific disease. For example Cancer. However one should consider that there are trigger factors that “activate” the disease. AS it is also evident that not all those that have a genetic predisposition to CA will indeed have it. Lung CA is a good example, because heavy smoking is the trigger.

Noteworthy is the fact that no link has been found between PHD3 (marker D14S1049) along with other candidate genes known to be involved with hypoxia sensing and erythropoiesis, erythropoietin, erythropoietin-receptor, HIF1a, Von Hippel-Lindau, propyl hydroxilase domain containing 1,2,3 and phosphatase and tensin homolog deleted on chromosome ten in CMS patients. (3)
Since CMS is a undefined disease, according to our experience without any genetical factor, CMS can be present and is more severe, in many types of respiratory and ventilatory disease. We are familiar with most of the CMS bibliography and we personally know the majority of the authors and cannot fail to notice that mistakes are often made, selecting patients with CMS that clearly had pulmonary disease (4).

This systematic mistake has lead the International Consensus Group to make a score for the classification of CMS. We strongly expressed our disagreement, CMS greatly differs from AMS which can indeed have a scoring system such as the Lake Louise, since it is acute and with limited symptomatology, being hypoxia the only trigger. At the conclusion of our international meetings (2) in several parts of the world and through the internet, we were invited by Jack Reeves to publish another paper expressing our points of view:

“Chronic Mountain Sickness: The reaction of physical disorders to chronic hypoxia”.(1)

Considering CMS has multiple ethiopathogenesis, hardly can one search for a specific gene. CMS when intensively examined present cardio-pulmonary pathologies that are often overlooked. To find a specific gene in children of one male parent with CMS, one could well be looking at a gene that gives rise to intrapulmonary shunts, or chronic bronchitis, or any other disease that in the hypoxic environment of high altitude would give rise to polycythemia (commonly know as CMS).

Hypoxia as a trigger of CMS, not only depends on hypoxia but likewise on the magnitude of the respiratory and ventilatory lesions. For example, a small pulmonary lesion will not give rise to CMS at 3000 m but will become evident above that altitude.

The children in this study are defined as subjects that will not adapt to high altitude, and this seems incongruent with the reality that they will indeed live on, to become adults at high altitude, just as their parents.

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http://altitudeclinic.com

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare I have no competing financial or other interests.

Prof. Dr. Gustavo Zubieta-Calleja