Reviewer's report

Title: A study of chronic mountain sickness in Chinese Han males who migrated to the Qinghai-Tibetan plateau: Application and evaluation of CMS diagnostic criteria

Version: 1 Date: 27 January 2014

Reviewer: Robert Naeije

Reviewer's report:

The authors report on the prevalence of chronic mountain sickness (CMS) in Chinese Han males who migrated to the Qinghai-Tibet plateau. The diagnosis of CMS was discussed with respect to the Qinghai scoring system. Based on the combination of a clinical diagnosis and a Qinghai score > 6, the incidence of CMS over a 2 to 96 month period of time was 17.8%. A binary logistic correlation analysis showed altitude, length of exposure to altitude, pulse oximetry SO2,(SpO2), heart rate, BMI, alcohol consumption AMS history and mean blood pressure were correlated with the incidence of CMS. A cluster analysis identified a hemoglobin (Hb) cut-off value of 20 g/dl for the diagnosis of excessive polycythemia, and showed the presence of a subgroups with high altitude “deterioration” without polycythemia. This is interesting. However, the paper is difficult to read because it is too long, in all its sections, the results are displayed with too much detail, but interesting data, such as for example how many subjects were with CMS symptomatology but Hb<21 g/dl difficult to find. Re-writing with substantial shortening will make the report much clearer.

Suggestions for improvement are listed below.

1. It is always a problem to use a scoring system for the purpose of diagnosis. Normally, a scoring system serves to measure the severity of a syndrome or disease having been diagnosed.

2. The authors have a point in proposing a bit lower cut-off value for Hb in men, 20 g/dl instead of 21 g/dl for a diagnosis of “excessive” polycythemia, but does it really correspond to the level needed to maintain oxygen delivery to the tissues? Or to the cut-off value of symptoms? Until this is clarified, the diagnosis of CMS will have to remain essentially based on expert consensus, as reported in ref 7.

3. The abstract should be clarified, with omission of interpretation statements in the “results” and a conclusion more tightly supported by the data. The interest of your report is in the high incidence of CMS as defined in ref 7 in recently immigrated Han Chinese and this over a relatively short period of time, and your cluster analysis.

4. Introduction. This section should be shortened to a maximum of one page, with omission of speculation about pulmonary hypertension and right heart failure as components of the CMS syndrome. Please revise your pathophysiological understanding regarding the cardiac component of CMS with more recent and generally accessible papers (Naeije R. JACC Cardiovasc Imaging. 2013;
A relative hypoventilation is an important component of CMS, but daytime PaCO2 is only slightly higher in CMS than in high altitude controls.

5. Introduction. Please state clearly the purpose of your study. As it is you apply a tool for an epidemiological-type of a study on CMS, but use the results to criticize it. So then, what is the gold standard to use?

6. Methods. Please clarify the statistical analysis and how you identified independent predictors of CMS.

7. Why were heart rate and blood pressure selected as possible predictors of CMS?

8. Results. Please summarize your findings in no more than 2 pages. Details in tables 4, 5 and 6 are redundant or superfluous. Please show the proportion of subjects with CMS symptomatology by Hb<21 g/dl. This is important for the validation of the Qinghai score!

9. Discussion. The first § has a statement about “oxygen equilibrium” which is rather obscure. But please summarize your main findings in 2 or 3 sentences.

10. Discussion, page 16 first §. The statement on how excessive Hb causes hypoxemia is unclear. Polycythemia causes an increase in pulmonary vascular resistance and a decrease in ventilation (with subsequent decrease in PO2, as predicted by the alveolar gas equation) (see refs above). Why polycythemia might later pulmonary gas exchange is entirely unclear.

11. Page 16, second §. The discussion about optimal cut-off value for Hb is confusing. Please refer to basic physiology, as summarized time ago by Lenfant and Sullivan, N Engl J Med 1971; 284: 1298-309 Modeling of optimal Hb on arterial O2 content at decreasing PO2 is a classical physiological exercise, already practiced by Otis and Rahn. Why ignore it?

12. Page 18. One of the reasons of “CMS symptoms” but a normal increase in Hb at high altitude is of course an excessive increase in pulmonary artery pressure, likely to occur in some 1 % of subjects (discussed in recent refs mentioned above). “HADT” is otherwise a hazy concept.

13. Page 19. The discussion about pre-disposing factors is excessively speculative, and should be omitted. Overlap of AMS and CMS is probably simply a matter of chemosensitivity, decreased in both. Length of high altitude stay was already discussed by Sullivan and Lenfant, and is all about the normal evolution of the ventilator response to hypobaric hypoxia over time. This evolution seems to be accelerated in acclimatized Han Chinese.

14. References. There are too many refs to books or articles difficult to find. Chapters of books may lack scientific validation, and should therefore be limited to one or two. Several refs are redundant (for example ref 4 and 6) or irrelevant (for example ref 14, - testosterone is globally irrelevant, refs 37 to 42, 50, 51, 53, 54,55,56,57 etc clearly out of the scope of the pape, etc). So the references list should be better limited to a maximum of 30 titles, preferably in peer reviewed accessible journals.
15. There are way too many figures. I would suggest only the fig showing symptom score vs Hb (1C and 1H) and fig showing symptoms as a function of time at altitude. (3K and 3L)

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I have no competing interests