“Cu, Pb and Zn serum concentrations in patients with Chronic Mountain Sickness”

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“Chronic Mountain Sickness or Monge’s Disease ”

• **Historical terms:**
  High-altitude excessive polycythemia or erythrocytosis, excessive erythrocytosis, high altitude pathologic erythrocytosis

• **Definition of the disease:**
  A clinical syndrome of gradual loss of acclimatization to life at high altitude. It is characterized by excessive erythrocytosis (females Hb ≥ 19 g/dl; males Hb ≥ 21g/dl), severe hypoxemia and in some cases moderate or severe pulmonary hypertension.
Respiratory characteristics in CMS

• High altitude natives or residents, breath deeply and have a lower PETCO$_2$ than sea level natives.

• CMS patients are relatively hypoxic and hypercapnic compared with HA natives.
Laboratory variables in healthy (HA) natives and patients with CMS (4,540 m)

<table>
<thead>
<tr>
<th></th>
<th>HA</th>
<th>CMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, g/dl</td>
<td>20.8</td>
<td>20.8 – 28.4</td>
</tr>
<tr>
<td>No. RBC, mill/mm³</td>
<td>6.2</td>
<td>6.5 – 10.0</td>
</tr>
<tr>
<td>Hct, %</td>
<td>59.9</td>
<td>55.0 – 93.8</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>81.4</td>
<td>59.6 – 80.0</td>
</tr>
<tr>
<td>PACO₂, mm Hg</td>
<td>32.5</td>
<td>35.0 – 45.6</td>
</tr>
<tr>
<td>HCO₃⁻, mM/l</td>
<td>20.9</td>
<td>23.4 – 28.4</td>
</tr>
<tr>
<td>pH, arterial</td>
<td>7.43</td>
<td>7.39 – 7.46</td>
</tr>
</tbody>
</table>

Monge M. y Monge C, 1966
Chronic Mountain Sickness
Hct: 84%
VE = f(SaO2) and hypoxic ventilatory response (AHVR, l/min,%); (n=25).

León-Velarde et al., JAP 94:1269, 2003
Ventilatory sensibility to CO₂ using the MFBS with 8 Torr changes from resting PETCO₂.

Fatemian et al., JAP 94:1279, 2003
Acute ventilatory response to CO₂ in CMS patients (n=9) – 3 weeks with ACZ - .

![Graph showing acute ventilatory response to CO₂](image)

- **250 mg/day ACZ**
  - **VE (l/min)**
  - **PETCO₂ (Torr)**

- **Pre-ACZ**
- **Post-ACZ**
Mean Pulmonary Arterial Pressure

- Lowlanders at sea level
- Tibetan 3658 m
- Andes 3690 m
- Andes 4260 m
- Han Chinese 3658 m
- Andes 4260 m

Mean Pulmonary Arterial Pressure (mmHg)
• Several high altitude populations work in mining activities.

• Metals affect important metabolic pathways and are constituents of several vitally important enzymes, which are related to control of breathing, as well as pulmonary vasoconstriction and/or hematopoiesis.
Subjects

- Case-Control study.
- 41 high altitude natives residents from Cerro de Pasco (4,300 m) without a history of ocupacional exposure to metals.
- 2 groups were studied:
  - 20 pacientes with moderate or severe score for CMS and hemoglobin (Hct) > 64 g/dl.
  - 21 controls healthy natives (Hct < 62 g/dl)

The metals measured were Cu, Pb and Zn
Copper

- Copper (Cu) = 0.7 – 1.4 mg/l

- Copper (Cu): SOD
  ceruloplamine transport Cu
  Cit C

Increase levels produce:
  » Inhibition of sulfidril groups
  » Hemolisis
  » Action in Fe absorption
Lead

• Lead (Pb): toxic > 10 mg/l
• Binds to sulphhydril groups producing:
  – Inhibition of acide δ- aminolevulinic deshidratase (ALAD) ALA accumulation
  – Inhibition coporfirinogene oxidase (biosynthesis inhibition of HEM)
  – Ferroquelatase inhibition (protoporf IX accumulation)
• Signal and nerve transmission impairment
• Zinc (Zn)= normal $\rightarrow$ 0.5 – 1.2 mg/l
Human carbonic anhydrase II, & zinc site

1st known zinc-containing enzyme, discovered 1932
At least, 7 Cas, each with its own gene, in humans

Zinc bound to imidazole rings of 3 His, and to $\text{H}_2\text{O}$ molecule
Functions of Zinc

- Cofactor to many enzymes
- Synthesis of DNA
- Protein metabolism, cell membrane
- Wound healing, immune function, growth
- Development of sexual organs and bones
- Insulin function
- Zinc finger proteins – gene regulation
- Component of superoxide dismutase
Methods for metal determination

• 50μl of blood - at 4°C – 7°C aprox. ambient temperature
  – Pb: Lead Care method.
  – Zn: atomic absorption.
  – Cu: atomic absorption.
## Characteristics of the CMS population (I)

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Hct</th>
<th>SaO2</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(years)</td>
<td>(%)</td>
<td>(%)</td>
<td>(beats/min)</td>
</tr>
<tr>
<td>C</td>
<td>42.13</td>
<td>55.66</td>
<td>87.86</td>
<td>75.25</td>
</tr>
<tr>
<td>CMS</td>
<td>44.37</td>
<td>69.15</td>
<td>85.67</td>
<td>75.15</td>
</tr>
</tbody>
</table>

*Significant difference with p < 0.0001 and p < 0.02*
### Characteristics of the CMS population (II)

<table>
<thead>
<tr>
<th></th>
<th>CMSs</th>
<th>Pb</th>
<th>Zn</th>
<th>Cu</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(mg/l)</td>
<td>(mg/l)</td>
<td>(mg/l)</td>
</tr>
<tr>
<td>C</td>
<td>6.55</td>
<td>6.81</td>
<td>0.47</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>4.48</td>
<td>3.17</td>
<td>0.14</td>
<td>0.28</td>
</tr>
<tr>
<td>CMS</td>
<td>10.35</td>
<td>6.21</td>
<td>0.94</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>3.53</td>
<td>2.81</td>
<td>0.52</td>
<td>0.16</td>
</tr>
</tbody>
</table>

* p<0.005, p<0.001
Hematocrit and serum concentration of Zinc
Metallothionein

*Metal Ion Homeostasis:* sequestering and transferring Zn, Cu, Cd.

*Antioxidant:*
- Elevated oxidative stress
- Intercepts $O_2^-$, HO·, ·NO, ONOO-
- Genetic manipulation studies show that MT can protects cells and tissues against oxidative and nitrosative damage.
MT -/- mice show no increase in labile zinc in response to hypoxia and have a blunted HPV.
Hypoxia increases labile zinc in the isolated perfused lung of MT wild-type mice

• Hypoxia induced increase in labile zinc in the endothelium of small diameter vessels is dependent of NO.

• Stimulation of the hypoxic mediated elevations in free Zn significantly increase HPV.

• Hypoxia-induced increases in NO synthesis contribute to HPV via formation of S-nitrosothiol in the metal binding center of MT and resultant changes in zinc homeostasis.