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TRIPLE HYPOXIA SYNDROME

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ABSTRACT

Many patients with **excessive erythrocytosis (EE)**, with hematocrit greater than 55%, but lower than 70%, apparently are normal. They work, play soccer, develop intellectual activities and frequently perform better than sedentary normal people (3500 m). They request medical attention, only when they present symptoms similar to those of **acute mountain sickness (AMS)**, such as: headache, dyspnea, nausea, lassitude and indigestion. Without going higher they have been said to experience "sorojchi (AMS) in bed". They show extreme hypoxia with an oxygen arterial tension (PaO_2) near 20 mmHg, with or without hypercapnia and a normal or acidotic pH. We have previously named this complication of **EE, as the triple hypoxia syndrome (THS)**. It is due to: [1] Normal high altitude adaptation to hypoxia, [2] EE hypoxia (CMS) and [3] acute hypoxia that can be reversed by oxygen. The THS is similar to "surviving" on the summit of Mount Everest. It may be caused by viral infections (flu) or some other acute respiratory disease, with malaise that lasts several days without treatment and typically is reversed by 24 hours of oxygen to PaO_2 baseline values of their chronic condition with EE. The diagnosis is important, since the THS is an acute transitory condition, that when not recognized and treated with oxygen can possibly lead to cardiac, pulmonary or cerebral complications. **(Acta Andina 1996, 5:15-18)**

RESUMEN

Muchos pacientes con eritrocitosis excesiva (EE), con hematocritos mayores a 55%, pero menores de 70% aparentemente se desarrollan normalmente. Trabajan, juegan fútbol, y desarrollan actividades intelectuales incluso en mejores condiciones que las personas normales sedentarias de la misma altura (3500m). Ellos solicitan atención médica, solamente cuando presentan síntomas similares a los del sorojchi o mal de altura, tales como: cefaleas, disnea, nausea, lasitud e indigestión. Sin ascender a la altura se dice que sufren "sorojchi en cama". Sus gases en sangre muestran extrema hipoxemia con tensiones parciales de oxígeno (PaO_2), alcanzando los 20 mmHg, con o sin hipercapnia, y pH normal o acidosis, Hemos denominado previamente a esta complicación de la EE, como **síndrome de triple hipoxia (THS)**, el cual se debe a la suma de las tres siguientes hipoxias: [1] hipoxia normal de altura, [2] hipoxia de la EE [3] hipoxia aguda reversible despúes de la administración temporal de oxígeno . La THS se asemeja a "sobrevivir" por encima de la cima del monte Everest. Puede deberse a infecciones virales (gripe) o alguna otra forma de enfermedad respiratoria aguda, con malestar que dura varios días sin tratamiento y típicamente se revierte con 24 horas de oxígeno a un PaO_2 basal de la EE. Su diagnóstico es importante, ya que el THS es un transtorno agudo, que si no es reconocido y tratado con oxígeno puede llevar a complicaciones cardiacas, pulmonares o cerebrales.**(Acta Andina 1996, 5:15-18)**

More than 10% of the adult population in the Bolivian Andes, above 3000m, have increased numbers of red blood cells (RBC), commonly described as increased polycythemia, secondary erythrocytosis or recently Excessive Erythrocytosis (EE). This pathological entity is secondary to pulmonary disease of various etiopathogenesis associated with a low inspired partial pressure of oxygen in hypoxic environments [4,13,14,15]. It is well known as chronic mountain sickness (CMS) or Monge's disease [7,8,9,10] characteristically present in patients of 40 years or older, overweight, with hypoventilation, low arterial oxygen tension, low oxyhemoglobin saturation and cyanosis with or without CO_2 retention. There are different grades of this disease, in relation to the extent of the pulmonary lesions and the individual susceptibility. It affects natives and all races. They work, play soccer, develop intellectual activities and frequently perform better than sedentary normal people.

Periodically, these patients have aggravations of their bothersome symptoms, which force them to consult a physician. The symptoms include intense headaches, loss of appetite, nausea and sometimes bleading from gastro-intestinal ulcers or the nose. They look more cyanotic and have to interrupt their daily activities. In these circumstances many physicians perform phlebotomies, as the only therapeutic alternative. Although controversial, it seems that the phlebotomy temporarily alleviates the symptoms, without an adequate explanation.

Previously, we have described the first case and named it **Triple hipoxia Syndrome** (THS) a complication of EE [2,12,13]. Here, we present further observations in three cases at 3600m, with an average barometric pressure (PB) of 495 mmHg.

Case 1

Patient NPC, male 49 years old, born and living in La Paz, (3600 m), weight 88.6 Kg, height 162 cms who three days before consultation caught a cold, with malaise and headaches that interrupted his work as a truck driver. Five years ago he had similar symptoms but not as intense. Two years previously, polycythemia was found in a routine check-up, and phlebotomy was performed, with no further examination or treatment.

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On physical examination, he was slightly overweight, cyanosis of the hands, face, mucous membranes and palpebral conjunctives was present and he was able to walk around without severe impairment. The face was swollen, the skin dropsy and he was oliguric. His blood pressure was 160/100 mmHg. The hematocrit was 78%, hemoglobin 25.4 gm% the RBC count 8.736.000 per cubic mm. The white blood cell count was 5500 with 69% neutrophils, 29% lymphocytes, 1% eosinophiles and 1% monocytes. The erythrocyte sedimentation rate was 0 mm, the first hour. Uric acid was 4 mg%. Serum protein electrophoresis
with albumin, beta and gamma fractions within normal limits, but alpha 1 and alpha 2 were slightly diminished. The urine analysis was normal.

The electrocardiogram showed a small increase in P-wave amplitude and a left posterior hemiblock, typical of chronic cor pulmonale. The chest x-ray revealed a discrete increased hearth volume (+), pulmonary arch slightly prominent and an increase of the bronco-vascular shadows. Vital capacity in BTPS was 5024 ml (normal expected), FEV.1/FVC was 81%. The ventilatory and blood gas values are given in Table 1. PaO_2 before treatment was 20 mmHg.

		PIO2 mmHg	Hb gm%	VE(BTPS) ml/min	RF /min	VT ml	PaO2 mmHg	PaCO2 mmHg	pH art	CaO2 vol%
A	NORMAL	94	16.0	8577	17	486	57	28	7.40	20.57
B	Typical CMS	94	21.0	8013	17	477	46	31	7.38	29.29
C	Case 1	94	25.4	8505	19	447	20	30	7.42	11.29
D	Case 1 w/O2	430	25.4	9739	5	1947	54	32	7.40	30.36
E	Case 2	94	25.0	9856	23	428	19	35	7.31	10.07
F	Case 2 w/O2	430	25.0	13935	29	480	82	26	7.47	33.36
G	Case 3	94	25.4	6838	24	284	47	28	7.40	28.95
H	Case 3 w/O2	430	25.4	7612	16	475	185	27	7.37	34.95

Table 1.A)Mean values found in normal subjects, B)Chronic mountain sickness C,E & G)Cases with THS in the acute phase. D,F & H Cases during the administration of 100% oxygen while the shunt test is performed; PIO2 = Partial inspired oxygen tension; VE = ventilation per minute; RF = respiratory frequency; PaO2 = Partial arterial oxygen tension; PaCO2 = Partial arterial carbon dioxide tension; pH = arterial pH; CaO2 = arterial oxygen content. PB = 495 mmHg at 3600 m.

Ventilation was measured during 15 minutes collecting expired samples in a Tissot along with radial blood samples for their analysis in a PHmk2 Radiometer acid-base analyzer. Prior calibration followed manufacture's recommendations. Ventilation was repeated having the subjects inspiring 100% oxygen from a Douglas bag, during 5 minutes. Twenty four hours following oxygen treatment through nasal prongs at 2 liters/minute, the PaO_2 breathing ambient air returned to baseline values of 44 mmHg. Chest x-rays did not show any changes after the oxygen treatment.

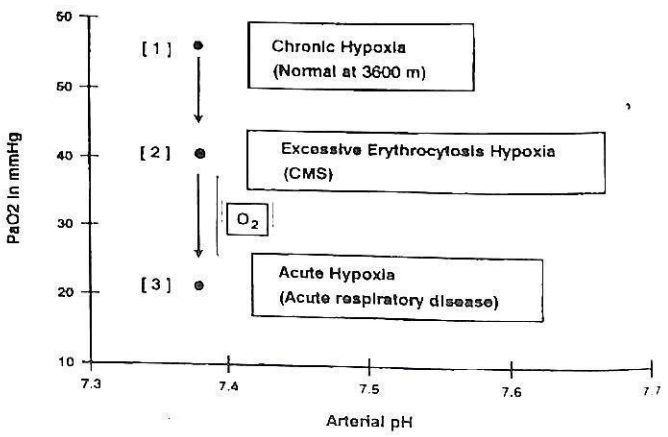

Fig 1. Triple Hypoxia Syndrome (THS). PaO2 showing the three levels of hypoxia. Twenty four hours of oxygen by mask reverse the THS to level 2.

Case 2

Patient CGG, male, 63 years old, born and living in La Paz, weight 92.4 Kg, height 168cm was diagnosed as having increased polycythemia several years earlier. On consultation he had fever, vomiting, dorsalgia and pain in both legs. One year before, he had a similar problem, and had to be hospitalized. On two occasions, he had had phlebotomies, the last one month before consultation. Four years before he had

had an episode of gastro-duodenal bleeding. He had never smoked. On physical examination, his tongue was white and he had tachycardia and cyanosis. His blood pressure was 174/103 mmHg. His hematocrit was 75% with 8,400,000 RBC`s and hemoglobin 25 gm%, white blood cell count was 9800, with 83% neutrophils, 15% lymphocytes, 1 %bands eosinophils. Urine analysis showed shown in Table 1. protein 500 mg/dl. His Vital Capacity in BTPS was 4330ml, normal expected, with a FEV.1/FVC of 97%. His blood gases are shown in table 1 along with ventilation studies. He had PaO_2 of 19 mmHg, $PaCO_2$ of 35 mmHg, pH of 7.31 and O_2 saturation of 29%. His ventilation studies following the same technique described in case one breathing ambient air and with 100% oxygen are shown in Table 1. The electrocardiogram with 125 beats/min showed elevated P-waves, negative T waves and left posterior hemiblock. He received oxygen at 3 liters/min. The next day his PaO2 without oxygen was 35 mmHg and the day after 41 mmHg, when he was discharged . No phlebotomy was performed, and his chest x-rays remained unchanged.

Case 3

Patient GAQ, was a male, 37 years old, 51 Kgs weight and 157 cm tall. He felt dyspneic, and had headaches. He had been diagnosed as having pulmonary tuberculosis 16 years before, and received adequate treatment. On consultation he was dyspneic and cyanotic. His tongue was white and his blood pressure was 105/80 mm Hg. His chest x-ray had many nodular callificcations and remained unchanged after treatment.

His hematocrit was 81% with 9.072.000 red blood cells per mm. and 27 gm% hemoglobin. His white blood cell count was 5250 with 64% neutrophils, 2% band, 1% eosinophils, 32% lymphocytes and 1% monocytes. Urine analysis showed protein 350 mg/dl. The electrocardiogram showed an elevated P-wave, with left ventricular hypertrophy. His vital capacity was 3709 ml (normal expected) with a FEV.1/FVC of 74%.His blood gases were: pH=7.35, $PaCO_2$ = 32 mmHg and PaO_2 = 47 mmHg with a calculated O_2 Saturation (SaO_2) of 82%. Following 24 hr oxygen therapy, his pH returned to 7.38 and PaO_2 increased to 52 mmHg (SaO_2 = 87%), at room air. Ventilation results are

Discussion

These patients have symptoms similar to those present in acute mountain sickness (AMS), which are headaches, loss of appetite, nausea and malaise [5,6] with the absence of respiratory alkalosis instead hypoventilation and a tendency towards acidosis. The syndrome resembles the ascent of a normal subject to altitudes above the summit of Mount Everest, where the PaO_2 is near 28 mmHg [11]. Hence the name "sorojchi (AMS) in bed". The low levels of PaO_2 near 20 mmHg reached by some, can only be explained by the increase of oxygen content in the blood of these patients with hematocrits above 80%. At sea level, such intense hypoxemia would be classified as acute respiratory failure [1] and would be treated in an intensive care unit [3]. Acute respiratory failure is not evident in these ambulatory patients at high altitude. The normal pH of 7.4 in one of these cases shows the remarkable capacity to compensate acid-base equilibrium in chronic hypoxia. Although the triple hypoxia syndrome (THS) was initially described as having a hematocrit of 80% or more, normal pH, $PaCO_2$ of around 30 mmHg and a PaO_2 of 20 to 30 mmHg [12], further observations show that different patterns exist. The acute lowering of the PaO_2 appears to be the most significant finding. In some cases, the pH has been observed to be below 7.34 and the $PaCO_2$ above 32 mmHg, as in case 3.

The symptoms seem to disappear following the administration of 24 hours of 2 liters/min of oxygen by mask. The PaO_2 returns to baseline values of their chronic condition with EE.

Further study is required to analyze about the possibility that the hematocrit increases acutely during THS, which may be probably atributed to hemoconcentration. It later decreases by approximately 4%, following 24 hours of oxygen therapy.

We believe that this acute transitory condition, ocurring with seasonal or climatological changes, coincides with influenza epidemics, or some other acute respiratory illnesses usually of viral origin, evident in all three cases. The Triple Hypoxia Syndrome is due to the addition of the 3 hypoxias: (1) Normal high altitude chronic hypoxia, (2) EE

hypoxia (CMS) and (3) acute disease hypoxia (Fig. 1). The third hypoxia is an essential cause of complaint in patients with EE and reversible at the same altitude after 24 hour oxygen administration, avoiding unnecessary phlebotomies frequently used.

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