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THE LEVELS OF SERUM CORTISOL IN HIGH ALTITUDE PULMONARY OEDEMA – IS IT THE CAUSE

Endocrinology

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ABSTRACT

Background: Cortisol is a physiological stress hormone and response of cortisol to high altitude exposure is dynamic influenced both by duration of exposure and exertion. It steadily increases following high altitude exposure or exercise and gradually plateaus on prolonged stay in high altitude areas. The variations in physiological cortisol response may have a pathological influence on High Altitude Pulmonary Oedema (HAPO) development. This study was carried out to test whether individuals who developed HAPO had a poor physiological stress cortisol response on exposure to high altitude.

Methods: Thirty patients admitted with HAPO along with thirty healthy controls who rapidly ascended to a high altitude were recruited in the study. The serum cortisol levels was estimated at the time of admission with HAPO and from healthy controls on 2nd or 3rd day of high altitude induction. The subjects (both patients and controls) were also subjected to ACTH stimulation test to determine adequacy of stress cortisol response as results of initial cortisol assay were not available. All subjects with one hour post ACTH cortisol response <18 g/dL or incremental cortisol rise <9 g/dL were diagnosed as having poor cortisol response.

Results: The study carried out on two comparative groups showed no difference in basal or Post ACTH cortisol on exposure to high altitude in patients who had developed HAPO from those who did not. The mean increment in serum cortisol or the Delta cortisol was also similar between two groups. The beneficial effect of Dexamethasone in HAPO is not due to relative adrenal insufficiency but due to its potent anti-inflammatory effects, enhanced alveolar fluid clearance and stabilisation of pulmonary endothelial membranes.

Conclusion: The altitude-induced rise of many hormones provides evidence that acute exposure to hypoxia tends to stimulate the neuroendocrine system. The serum cortisol levels in our study showed no difference in HAPO patients and the controls. Although drugs are frequently used to prevent or treat high altitude illness, the primary recommendation to decrease its incidence is staged/gradual ascent and progressive acclimatization while cornerstone of its treatment by gradual and passive descent to lower altitude and oxygenation. The steroids only act via its potent anti-inflammatory effects, enhanced alveolar fluid clearance and stabilisation of pulmonary endothelial membranes.

KEYWORDS

High Altitude Pulmonary Oedema (HAPO), Cortisol, Post ACTH Cortisol, High altitude

INTRODUCTION

High altitude is generally considered as height of 2500 m or above mean sea level while extreme high altitude is height more than 5500 m (1). A large number of people are exposed to high altitude which include for sporting purposes like skiing, mountaineering or for pilgrimages and also on duty in these areas. The various risk factors for these high altitude illness include maximum altitude reached, speed of ascent, poor acclimatization, physical exercise, re-exposure to HA environment after staying in low altitude area, predisposing genetic factors, previous such history of HA illness, intake of any sedatives or recent infections affecting the lower airways (2). The other contributing factors include prevailing weather conditions like low ambient barometric pressures resulting in hypobaric hypoxia, low temperatures, high wind velocities and drier air (3).

HAPO which is non-cardiogenic pulmonary oedema is one of the most common diseases responsible for most high altitude deaths (4). It involves both genders and classically occurs on 2nd or 3rd day at high altitude. It occurs due to extravasation of fluid, plasma proteins and blood cells into the interstitial and alveolar spaces due to the combination of increased cardiac output and pulmonary hypertension and elevated capillary pressure as a result of hypobaric hypoxia. The decreased bioavailability of nitric oxide and impaired sodium and water transport in the lung might cause elevated pulmonary artery pressure and contribute to pathogenesis of HAPO (5-9).

Cortisol is a physiological stress hormone and response of cortisol to HA exposure is dynamic influenced both by duration of exposure and exertion. It steadily increases following high altitude exposure or exercise and gradually plateaus on prolonged stay in high altitude areas. Most workers have found a rise in cortisol at rest at high altitude (10-12) with return to baseline of cortisol with prolonged exposure but not all workers have found this rise in cortisol at high altitude (13-15) and no rise following moderate exercise. It would therefore seem appropriate that, as before, variations in cortisol response may have a pathological influence on high altitude illness.

Since there are few and inconsistent results to base any sound conclusion, we sought to test whether individuals who developed HAPO had a poor physiological stress cortisol response on exposure to high altitude.

MATERIALS AND METHODS

Thirty patients admitted with HAPO along with thirty healthy controls who had similarly rapidly ascended to a high altitude were recruited in the study. High-altitude pulmonary oedema was clinically suspected with presence of each of 2 out of 4 symptoms (dyspnoea at rest, cough, weakness or decreased exercise performance and chest tightness or congestion) and signs (tachycardia, tachypnoea, central cyanosis and audible crackles or wheezing in at least one lung field) and later confirmation by chest radiograph showing interstitial or alveolar infiltrates in atleast one quadrant and characteristic absence of kerley B lines and cardiomegaly. The serum cortisol levels were estimated at the time of admission with HAPO in patients and healthy controls on 2nd or 3rd day of high altitude induction. The subjects (both patients and controls) were also subjected to ACTH stimulation test to determine adequacy of stress cortisol response as results of initial cortisol assay were not available. ACTH Stimulation Test is done by injecting 25 units of Synthetic ACTH (Acton Prolongatum) intramuscularly (equivalent to 250 g of ACTH) and blood sample was collected after 60

min for estimation of cortisol. All subjects with one-hour post ACTH cortisol response <18 g/dL or incremental cortisol rise <9 g/dL were diagnosed as having poor cortisol response (16). Serum for cortisol estimation was separated in all subjects and stored at -60°C till cortisol assay. The cortisol assay was performed using radioimmunoassay kit (Immunotech, Beckman Coulter Company) using Startec SR300 automated radioimmunoassay system.

Inclusion criteria

The inclusion criteria were patients admitted with HAPO and healthy controls who had similarly rapidly ascended to a high altitude in the absence of any other medical illnesses.

Exclusion criteria

The exclusion criteria were acute illness causing physiological cortisol increment, cardiogenic or toxic pulmonary oedema, adrenal or pituitary disease or on prophylactic dexamethasone therapy or on any other medications.

Results

This study was carried out in 30 patients admitted with HAPO and 30 healthy controls who had similarly rapidly ascended to a high altitude. There was no significant difference in age of both groups (24.2±6.2 vs. 23.9±7 years, p value) and all were males. Basal and post ACTH serum cortisol were within normal range in both patients who had developed HAPO and in healthy control group. Basal cortisol ranged from 4.23-11.47 µg/dl in patients and 4.62-10.82 µg/dl in controls. The post ACTH serum cortisol ranged from 18.86-39.36 µg/dl in patients and 19.20-36.66 µg/dl in controls. Mean increment in cortisol after ACTH was 14.26 – 22.65 µg/dl in patients and 15.13 – 24.87 µg/dl in controls.

There was no difference in basal serum cortisol or Post ACTH cortisol on exposure to high altitude in patients who had developed HAPO from those who did not.

Table: Basal, Post ACTH and Incremental Cortisol levels in Patients and Controls at High Altitude

Variable	Patients (n=30)	Controls (n=30)	P value
Age (yrs.)	24.2±6.2	23.9±7	0.86
Basal Cortisol (µg/dl)	4.23-11.47	4.62-10.82	0.88
Post ACTH Cortisol (µg/dl)	18.86-39.36	19.20-36.66	0.63
Incremental Cortisol Post ACTH (µg/dL)	14.26 – 22.65	15.13 – 24.87	0.19

(p value less than 0.05 is statistically significant)

DISCUSSION

High altitude pulmonary oedema, although specific and restricted to persons going to high altitude can prove lethal, if left untreated. Timely treatment of HAPO depends on its timely diagnosis. The most reliable and effective treatment for HAPO is gradual and passive descent to lower altitude, since physical exertion is likely to exacerbate HAPO, oxygenation or alternatively use of hyperbaric chamber. If evacuation to a lower altitude is unsafe or impossible then continuous positive airway pressure / oxygenation decreases pulmonary hypertension and vasoconstriction and thus extravascular fluid accumulation (17).

The pharmacological therapies include Nifedipine, a Ca^{2+} channel antagonist which acts as a vasodilator on both systemic as well as pulmonary circulation (18), selective pulmonary vasodilator Tadalafil (a phosphodiesterase-5 inhibitor) by increasing endothelial nitric oxide synthase and Dexamethasone with multitude of effects that include stimulation of alveolar sodium and water reabsorption, enhanced nitric oxide availability in pulmonary vessels, improved surfactant production and tightening of pulmonary capillary endothelium by decreasing the monocyte chemoattractant protein-1 level, thus preventing an inflammatory response to hypoxia, inhibiting vascular endothelial growth factor–induced angiogenesis and modulation of increased sympathetic activity.

The serum cortisol levels in our study showed no difference in HAPO patients and the controls. Most workers have found a rise in cortisol at rest at HA but two other studies by Smith et al and Maher et al reported no rise in cortisol at 4300m and sea level (19). This return to baseline of cortisol with prolonged exposure is supported by others who found an initial rise in resting cortisol.

The recommendations of treatment with Dexamethasone is not due to relative adrenal insufficiency in patients developing HAPO but because of its potent anti-inflammatory effects, enhanced alveolar fluid clearance and stabilisation of pulmonary endothelial membranes.

CONCLUSION

The altitude-induced rise of many hormones provides evidence that acute exposure to hypoxia tends to stimulate the neuroendocrine system and adequate endocrine response can improve oxygen delivery via cardiorespiratory adaptations. This observational clinical study was carried out in HAPO patients and similar controls. The serum cortisol levels in our study showed no difference in HAPO patients and the controls. Although drugs are frequently used to prevent or treat high altitude illness, the primary recommendation to decrease its incidence is staged/gradual ascent and progressive acclimatization and treatment by gradual and passive descent to lower altitude and oxygenation which continues to be the cornerstone of the management of HAPO.

Conflicts of interest

All authors have none to declare.

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