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CLINICAL CASE

Reentry High-Altitude Pulmonary Edema in Pediatric Patients

Edema pulmonar de altura por re-ascenso en pacientes pediátricos

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What do we know about the subject matter of this study?

High-altitude pulmonary edema occurs in non-adapted people when ascending to altitudes above 2,500 masl, however, it can also occur in adapted people returning from low altitude areas.

What does this study contribute to what is already known?

We report six pediatric cases that required oxygen therapy due to high-altitude pulmonary edema after returning to 2,660 masl from low-altitude areas. We highlight its importance as a differential diagnosis in cases of pulmonary edema in high-altitude cities.

Abstract

High-altitude pulmonary edema (HAPE) occurs when a person without adequate pulmonary adaptation ascends above 2500 meters above sea level. Usually, it is more frequent among those living at low altitudes, however, it can occur in people who live at high altitudes and descend to lower ones for a short time, which is called re-entry HAPE. **Objective:** To describe the clinical course, diagnosis, and management of re-entry HAPE in pediatric patients, and to achieve an early approach to reduce complications. **Clinical Cases:** We present 6 cases of pediatric patients diagnosed with re-entry HAPE in a fourth level hospital in Bogotá, Colombia, between 2013 and 2018. All patients resided in Bogotá, 5/6 were male, the median age was 11 years, 4/6 had a history of lung disease, and 5/6 required a high-flow oxygen device. In all cases, the chest X-ray reported opacities and 2/6 showed pulmonary hypertension on the echocardiogram. All patients were initially treated for bacterial pneumonia or asthma and, although they progressed adequately, these inadequate treatments can cause complications. **Conclusion:** The diagnosis, treatment, and prevention of HAPE are important since it is usually confused with infectious pulmonary pathologies due to its similar clinical course, which leads to inadequate treatment and can generate complications. The suggestion is that HAPE should be considered as a differential diagnosis in patients with a recent history of ascending to high altitude cities.

Keywords:
Pulmonary Edema; Altitude Sickness; Pulmonary Hypertension; Hypoxia

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Introduction

High-altitude pulmonary edema (HAPE) is a non-cardiogenic pulmonary edema that occurs due to acute exposure to hypobaric hypoxia caused by a rapid decrease in atmospheric pressures[1,2]. This condition affects susceptible subjects who do not achieve an adequate pulmonary adaptation when ascending to more than 2,500 meters above sea level (m.a.s.l.). It has been observed that this pathology is more frequent in people who live at low altitudes when ascending rapidly to higher altitudes[3], however, and although less frequent, some people who have lived for years at high altitude and descend to lower altitudes for a short period, may develop HAPE when ascending again; named re-ascending HAPE[4,5].

The worldwide incidence of classic HAPE varies from 0.01% to 31% depending on the series[6]; however, the incidence of classic and re-ascending HAPE in the Andes is unknown. On the other hand, studies on HAPE show that the pediatric population between 2 and 20 years of age is more susceptible to changes in altitude[7], although the incidence in this age group is not known, thus making it a very poorly documented disease.

HAPE usually manifests during 2 to 4 days after ascent, frequently starting during the night. Its symptoms are dyspnea, weakness, and dry cough that progresses to productive cough, and on the physical examination patients present fever, tachycardia, tachypnea, and lung pain. Diagnostic images may show alveolar opacities and alteration of the pulmonary parenchyma, causing that HAPE can be easily confused with a pulmonary infectious process when health personnel is unaware of the existence of this pathology, that leads them to perform incorrect antibiotic management, which is very frequent in the hospital sphere[2,4].

Classic or re-ascending HAPE are rare diseases but of great clinical significance in countries with a wide variety of geographical areas where it is quite easy to change altitude quickly. Most studies of this medical condition are directed towards people who present classic HAPE but many patients present re-ascending HAPE, which, due to its poor documentation is often underdiagnosed, and therefore patients do not receive adequate management.

The objective of this study is to describe the clinical course, diagnosis, and management of HAPE, in order to alert medical personnel of this diagnostic possibility and to achieve an early approach to reduce complications due to inadequate treatment.

Clinical Cases

We describe 6 clinical cases of pediatric patients diagnosed with re-ascending HAPE between 2013 and 2018 in a fourth-level hospital in Bogota, Colombia. Five patients were male and the median age was 11 years (interquartile range [IQR] 3). Four of the cases reported history of respiratory pathology requiring hospitalization such as pneumonia, bronchiolitis, asthma, or obstructive sleep apnea. All the patients lived in Bogota (2,640 m.a.s.l.), so by knowing the place of displacement (median altitude 326, IQR 254 m.a.s.l.), it was possible to diagnose re-ascending HAPE given that all locations were at a lower altitude than Bogota. Table 1 shows the other general characteristics of the cases.

Five of the six patients required management with high-flow oxygen therapy in the pediatric intensive care unit (PICU) due to severe hypoxemia and respiratory distress. In the laboratory studies, arterial blood gases were measured in only one patient which showed respiratory acidosis (pH 7.30; PCO_2 34.6 mmHg) with oxygenation disorder (paO2/FiO2 205; SpO2/FiO2 303), and hyperlactatemia (4.5 mmol/L). The other patients did not require oxygen support, but their median admission SpO2/FiO2 ratio was 284 (IQR 165). In 3 cases, a complete blood count was requested, which was within normal limits; however, one patient had a report from another institution of a complete blood count with severe leukocytosis (40,000 cells/mm^3). In all cases, the chest X-ray showed parenchymal opacities (table 2) and 2 of the 6 cases presented pulmonary hypertension in the echocardiogram.

Half of the patients were first diagnosed with infectious lung disease and treated with antibiotics and one of these cases was diagnosed with an asthmatic crisis due to the patient's history and was managed with corticosteroid and bronchodilator. The initial management was suspended after diagnosing re-ascending HAPE and the patients received the appropriate management with exclusive use of oxygen supplementation as needed, all with rapid responses and short evolution of the disease (median hospital stay 5 days, IQR 1). Table 3 details the previous management used.

In two of the cases, a control X-ray was performed 24 hours after, showing improvement of the pulmonary edema (figure 1). All patients evolved satisfactorily, and oxygen therapy was progressively withdrawn until hospital discharge.

Discussion

We present 6 cases of patients with high-altitude pulmonary edema due to re-ascent in which the diagnosis was not initially suspected, leading to unnecessary management, who presented good clinical evolution when therapies were withdrawn, allowing the disease to resolve spontaneously with the use of oxygen therapy.

Table 1. General characteristics of the patients

Travel feature	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Altitude of Origin *	2640	2640	2640	2640	2640	2640
Destination city	Campo alegre	Cartagena de Indias	Girardot	Santa Marta	Florencia	Yopal
Altitude of the city*	525	2	326	15	242	390
Altitude change *	2115	2638	2314	2625	2398	2250
Symptoms						
Symptom time	2 days	12 hours	1 week	1 day	2 days	1 day
Dyspnoea	+	+	-	-	-	-
Sputum	+	-	+	+	-	+
Cough	+	+	+	+	+	+
Chest pain	+	-	-	-	-	-
Cyanosis	+	+	+	-	-	+
Pulmonary rales or crackles	+	+	+	-	-	-
Shortness of breath	+	+	+	-	+	+
Polyypnea	-	+	+	-	-	+
Fever	-	-	+	-	+	-

*Meters above sea level.

This edema is caused by the rapid change in oxygen availability due to the change in altitude, which triggers a series of physiological processes upon exposure to hypoxia, among which are irregular and exaggerated pulmonary vasoconstriction, decreased release of vasoactive substances such as nitric oxide, decreased reabsorption of alveolar secretions, and increased sympathetic tone. All this causes pulmonary hypertension leading to interstitial fluid extravasation, producing pulmonary edema, and alteration of respiratory mechanics[3]. All these processes typically occur in people who live at low altitudes and who do not have a good pulmonary capacity to adapt quickly to these altitude changes, producing the classic form of this entity (classic HAPE).

Table 2. Report of diagnostic images

	Chest x-ray
Case 1	Diffuse alveolar infiltrates with right apical atelectasis
Case 2	Diffuse interstitial infiltrates in bilateral upper lobes
Case 3	Diffuse cottony alveolar opacities
Case 4	Diffuse alveolar infiltrates
Case 5	Right basal reticular interstitial pattern without consolidation
Case 6	Homogeneous opacities involving almost the entire right hemithorax with partial effacement of the right phrenic cost angle and pseudonodular infiltrates in both lung fields (Figure 1)

Table 3. Treatments received prior to diagnosis and hospital stay

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Oxygen	Yes	Yes	Yes	Yes	Yes	Yes
Furosemide	Yes	Yes	Yes	Not	Not	Not
Corticoid	Not	Not	Not	Not	Yes	Yes
Beta agonist	Not	Not	Not	Not	Yes	Yes
Antibiotic	Not	Not	Yes	Not	Yes	Yes
Hospital stay (days)	4	4	6	4	5	5

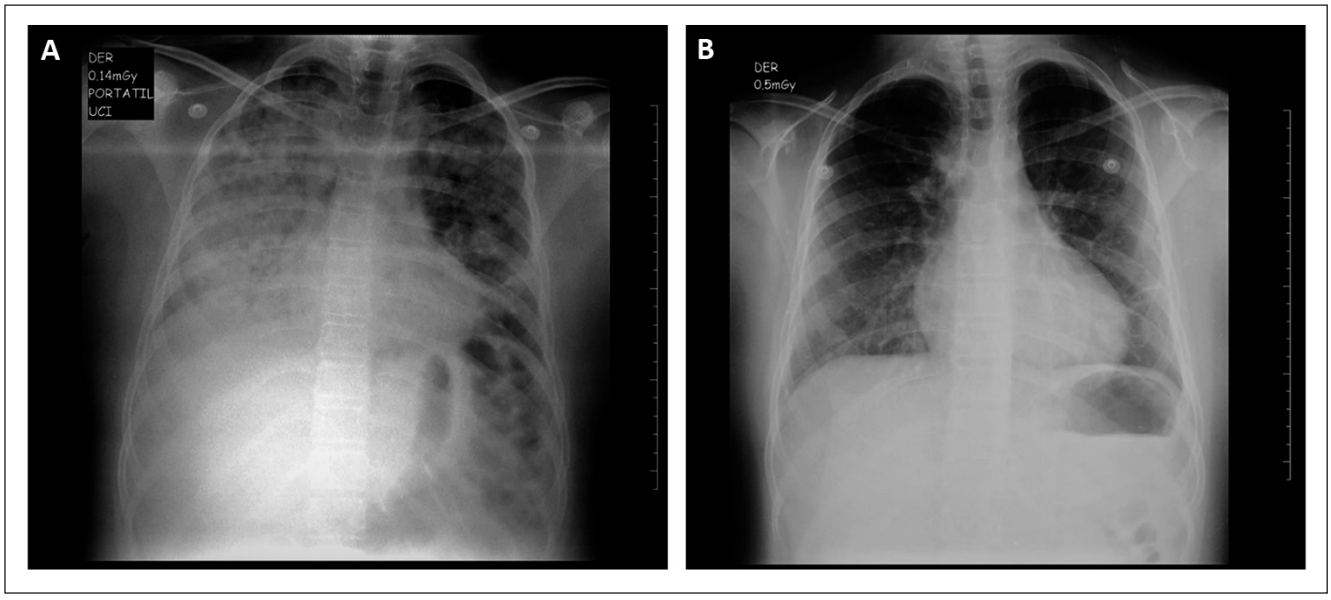

Figure 1. Case 6, image A shows the admission radiograph showing homogeneous opacities in the right hemithorax with partial effacement of the right phrenic cost angle and pseudonodular infiltrates in both lung fields. Image B shows the control radiograph taken at 24 hours, which shows improvement in pulmonary opacities with persistence of these at the bibasal level.

In the case of re-ascending HAPE, which occurs in patients with adequate pulmonary adaptation time, it has been proposed that the vascular smooth muscle of the pulmonary capillaries that protects against hypoxemia involves during the time that the individual remains at low altitude, thus depriving her/him of the adaptive mechanisms to tolerate high altitudes[8,9]. Another theory points to blood volume since prolonged exposure to high altitudes generates an increase in red blood cells which decrease at low altitudes generating a compensatory increase in plasma volume, which may explain pulmonary edema upon return to high altitudes[10]. Likewise, it is known that this clinical condition is more frequent in pediatric age since they have an increased pulmonary artery muscle tone, so vasomotor activity is greater, making them more hyperactive to pressure changes than adults[8].

Several studies report that patients with history of perinatal hypoxia, previous pulmonary pathologies such as viral infections, or congenital anatomical alterations that increase pulmonary pressure may predispose to the presentation of HAPE[8,9,11,12], which is consistent with our cases that had history of pulmonary disease and required hospitalization such as pneumonia, bronchiolitis, asthma or obstructive sleep apnea syndrome, which may be related to the development of HAPE in these patients.

HAPE is diagnosed according to the Lake Luise consensus criteria (1991), which include symptoms such as dyspnea at rest, cough, weakness or decreased exercise tolerance, and signs such as wheezing or crackles in at least one lung field, tachypnea, or tachycardia with history of recent travel[3,5]. The diagnosis should meet at least 2 symptoms and 2 signs, however, the manifestations of re-ascending HAPE can be more nonspecific such as headache, lethargy, memory alteration, and lack of sleep, evidencing cyanosis and plethoric facies[2]. On the other hand, these patients can present leukocytosis with neutrophilia[6] as did one of our cases and the chest x-ray showed findings similar to a pneumonic process, which makes its diagnosis more difficult. This explains why in half of the cases in this report, an initial diagnosis other than HAPE was made, however, due to the clinical evolution, the place of residence, history of recent travel to places of lower altitude, inconclusive laboratory test for infection, radiological images compatible with findings of pulmonary edema, radiological improvement in the following 24 hours, which is characteristic of HAPE[10], and the good response to the withdrawal of the initial management, the diagnosis of re-ascending HAPE was achieved.

The treatment does not differ between classic and re-ascending HAPE. The most evidence indicates the real descent of altitude and in case it is not possible, the simulation of the descent with hyperbaric therapy or with supplemental oxygen supply in order to reduce pulmonary arterial pressure[1,5,6], which explains the clinical improvement of all patients when managed with high-flow oxygen therapy. In 3 cases, the patients received furosemide with no complications, however,

the literature refers that management with diuretics is controversial, since it can help in the elimination of extracellular liquid, its adverse effects are greater, so its routine use is not recommended[1,2,5].

Regarding the prognosis, it is known that patients who present HAPE at some point in their lives are more susceptible to changes in altitude[3,5], therefore a slow ascent is recommended to allow pulmonary acclimatization[3]. Medications such as nifedipine can also be used, which generates pulmonary and systemic vasodilation, however, due to sympathetic activation at high altitudes, the effect on the systemic circulation is minimal[5]. The recommended dose is 1-5 mg/kg/day every 8 hours for pediatric patients[2], starting 1 day before ascending and up to 2 days after reaching the destination[5,9]. The use of other drugs such as beta2-agonists, selective phosphodiesterase-5 inhibitors, and carbonic anhydrase inhibitors has been proposed with apparently satisfactory results; however, the study samples are small and there are no studies in the pediatric population, so they should be used with caution[3,13]. Finally, if the child is suffering from a respiratory infection at the time of ascent, it is recommended to delay the trip until the acute symptoms are resolved[9].

Conclusion

Timely diagnosis, which includes asking about trips to other altitudes in acute cases of pulmonary disease with hypoxemia, adequate treatment (oxygen therapy support according to severity, usually with high-flow oxygen administration as they are well tolerated), and prevention of re-ascending HAPE (avoid rapid ascents in susceptible patients) are important since it is usually confused with infectious pulmonary pathologies due to their similar clinical course, which leads to inadequate treatment and can generate complications. It is suggested that, in patients with a recent history of ascent to high altitude cities, it should be considered as a differential diagnosis.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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