

Severe acute reentry high altitude pulmonary edema in pediatric patients: report of three cases and literature review

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ABSTRACT

Background. High Altitude Pulmonary Edema (HAPE) is a fatal form of severe high-altitude illness. It is a form of noncardiogenic, noninfectious pulmonary edema secondary to alveolar hypoxia. The exact incidence of HAPE in children is unknown; however, most literature reports an incidence between 0.5-15%. There are three proposed HAPE types including classic HAPE, reentry HAPE, and high-altitude resident pulmonary edema (HARPE).

Case. We present three pediatric patients who were diagnosed with re-entry high altitude pulmonary edema and did not have any underlying cardiac abnormalities. All patients reside in areas of high altitude with a history of travelling to places of lower altitude. They had respiratory infections prior to the manifestation of HAPE.

Conclusions. These are the first reported cases of children with reentry HAPE in Saudi Arabia. Reentry HAPE can occur in otherwise healthy children. Rapid ascent to high altitude and recent respiratory infections are the most commonly reported triggers. Prognosis is very favorable with a very rapid response to oxygen therapy. Education about HAPE is mandatory for families and health care workers working in high altitude areas.

Key words: high altitude pulmonary edema, children, re-entry HAPE.

High Altitude Pulmonary Edema (HAPE) is a fatal form of severe high-altitude illness. It is a form of noncardiogenic, noninfectious pulmonary edema secondary to alveolar hypoxia. Dyspnea on exertion, dry cough, followed by dyspnea at rest, and chest crackles that happen after a rapid ascent for more than 2500 meters are the common clinical manifestations of HAPE.¹⁻⁴ However, HAPE has been reported in patients with underlying cardiac diseases at an altitude as low as 1400 meters.⁵ There are three proposed HAPE types including classic HAPE, reentry HAPE, and high-altitude resident pulmonary edema (HARPE). Classic HAPE occurs in people

who live in low altitude areas and travel to high altitude, while reentry HAPE happens in people living in high altitude, returning from travels near sea level.⁴ HARPE happens without changing altitude, and respiratory infections are the usually obvious trigger.² In addition, genetic polymorphisms have been reported as a critical factor of HAPE predisposition.^{6,7} The exact incidence of HAPE in children is unknown; however, most literature reports an incidence between 0.5-15%.³

The risk of HAPE increases with rapid ascent above 2500 meters, recent respiratory tract infection, previous HAPE episode, and male sex. The underlying pathophysiology is an increase in pulmonary artery pressure, secondary to hypoxic pulmonary vasoconstriction, which results in leakage of fluids into the alveolar spaces.^{3,8} As per the Lake Louise diagnostic

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criteria for HAPE, a recent gain in altitude associated with at least two of the four typical symptoms (dyspnea at rest, cough, weakness/decreased exercise performance, and chest tightness/congestion) and at least two of the four typical signs (crackles/ wheezes, central cyanosis, tachypnea, and tachycardia) are suggestive the diagnosis of HAPE.¹ In addition, the chest radiograph is mandatory to confirm the diagnosis, which mainly shows bilateral opacities.⁴ If HAPE is left untreated, it can progress to severe respiratory failure and a mortality rate of up to 50%. Unfortunately, HAPE is commonly misdiagnosed as pneumonia or asthma.⁹ Herein, we report three cases of severe reentry HAPE, which are the first reported cases from Saudi Arabia to the best of our knowledge.

Case Reports

Patient 1

A 9-year-old female presented to the emergency room with acute onset of shortness of breath and cough for a 12-hour duration that happened after arriving at Abha city (her residential area 2200 Meters above sea level) from sea level area (Tehama area). There was a history of mild upper respiratory infection symptoms, fever, mild cough, and sore throat. She had a history of two similar episodes requiring hospitalization, with the average hospital stay being 2-3 days. She was in third grade and had good school performance. The patient was fully immunized. She also reported intermittent snoring and morning headaches for almost a year. She scored 15 out of 22 in the on The Sleep Related Breathing Disorder (SRBD) scale. SRBD scale is a validated pediatric sleep questionnaire that was described by a group of experts in pediatric sleep medicine with good sensitivity and specificity for obstructive sleep apnea diagnosis.¹⁰ According to the publishing group, a score of 7 out of 22 has most frequently been used as diagnostic of OSA.¹⁰ Physical examination showed she was in acute distress and severe hypoxia with SpO₂ of 35% at room

air; heart rate was 175 beats per minute, blood pressure was 120/ 72 mmHg (normal for age). Her weight was 51 kg above the 95th percentile. Her lung exam revealed bilateral diminished air entry with diffuse inspiratory crackles. Chest x-ray on admission (Fig. 1a) showed bilateral patchy opacities. Echocardiography showed normal heart function and structure without pulmonary hypertension which was done on day 2 of admission. Laboratory tests are summarized in Table I. She was admitted to the pediatric intensive care unit (PICU), started on High Flow Nasal Cannula (HFNC) running at 15 liter per minute (LPM) due to persistent hypoxic respiratory failure, and treated for presumed severe asthma exacerbation. She was started on continuous Albuterol nebulizer and intravenous (IV) methylprednisolone.

The pediatric pulmonary team was consulted. The patient was diagnosed with re-entry high-altitude pulmonary edema (reentry HAPE) given her past medical history, traveling to high altitude areas, and good response to oxygen therapy. On the second day of admission, the patient's symptoms improved, and was able to tolerate oxygen support at 2 LPM via nasal cannula. On the third day, she was discharged home on RA with normal heart rate, and significant improvement of patchy opacities on chest x-ray (Fig. 1b). Parents were instructed to monitor SpO₂ when returning to high altitude from low altitude and, if SpO₂ was less than 92% on RA, they were advised to start oxygen therapy immediately. After 18 months, she has been doing well without any episodes of HAPE. Informed consent was taken from patient and patient's parents.

Patient 2

An 11-year-old boy, twin A, from Abha (specifically AlSouda 3,015 m above sea level) presented with a one-day history of progressive dyspnea and productive cough, two days after returning from the city of Jizan (sea level) to Abba. The family spent their winter vacation (three weeks) in the Jizan area. Before traveling back to Abha, the mother reported

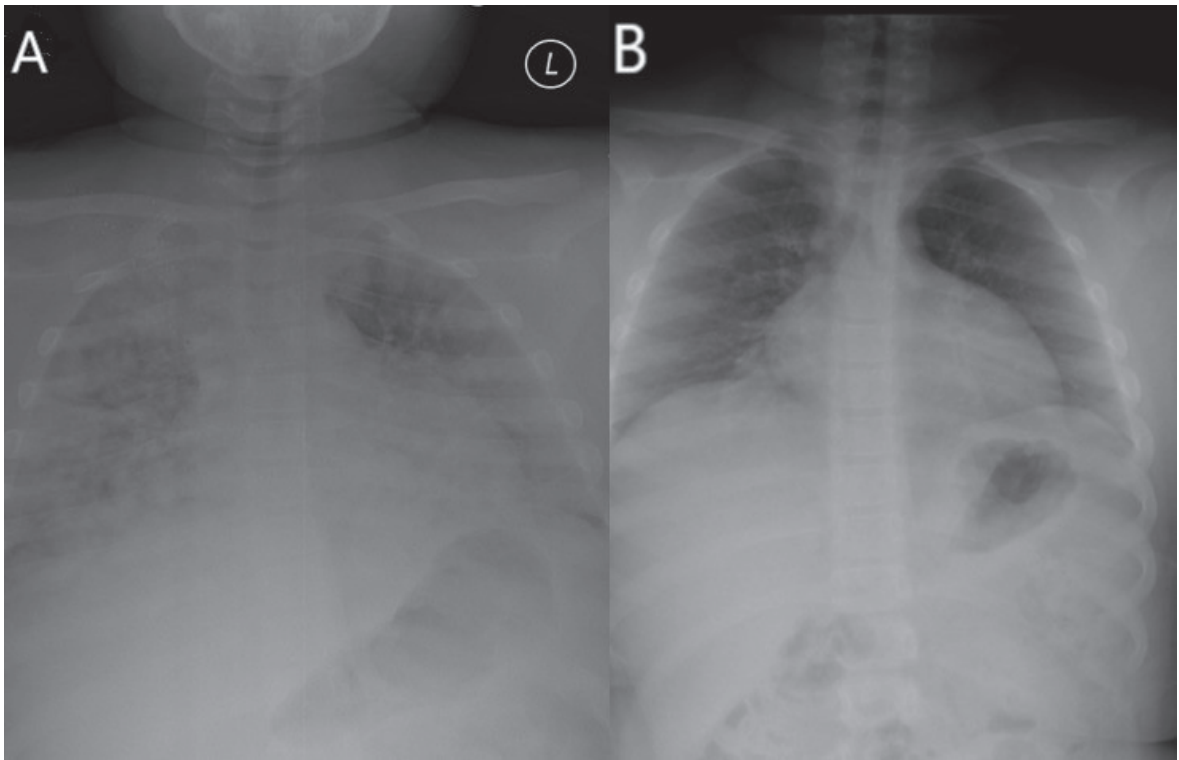


Fig. 1. Chest x-ray upon admission (A) and prior to discharge (B) for Patient 1.

Table I. Clinical characteristics, laboratory results and hospital outcome measures for the patients.

Variables	Patient 1	Patient 2	Patient 3
Age in years/sex	9/F	11/M (twin A)	11/M (twin B)
Clinical characteristics			
- Previous similar illness	+	-	-
- Recent respiratory infection	+	+	+
- Dyspnea	+	+	+
- Chest pain	-	-	-
- Initial ER ^a SpO ₂ ^b	37%	79%	63%
- Altered mental status	+	-	-
Laboratory results			
- WBC ^c (4-11x10 ³ /ul)	21.21	6.71	8.99
- Hb ^d (12-16 g/dl)	12.4	15.4	15.6
- HCT ^e (%)	37.1	46.4	47.2
- Echocardiography	Normal	Normal	Normal
Therapies and Hospital outcome			
- Asthma therapies	+	+	+
- Broad spectrum antibiotics	+	+	+
- Duration of oxygen therapy	24 hours	36 hours	36 hours
- Length of stay (days)	3	3	3

^a ER: emergency room; ^bSpO₂: oxygen saturation; ^c white blood cell counts; ^d hemoglobin level; ^e hematocrit

a history of respiratory infection in all family members, but there was no history of contact with confirmed or suspected Coronavirus Disease 2019 (COVID-19) patients. His vital signs on admission to the emergency unit were a heart rate of 145 bpm, respiratory rate of 28 breaths/min, blood pressure of 110/ 65 mmHg, temperature of 36.5°C, and SpO₂ of 79% on RA. The lung examination revealed mild respiratory distress with crackles most commonly heard at lung bases. The throat examination revealed oropharyngeal erythema without tonsillar inflammation. Neurologically, the patient was fully awake with a Glasgow coma scale of 15/15. Laboratory tests are summarized in Table I. Chest x-ray revealed bilateral heterogeneous opacities that involved both lung fields (Fig 2a). He was admitted to the general pediatric ward with suspected COVID-19 pneumonia. The patient was placed on 4 liters of oxygen through a nasal cannula and started on broad-spectrum antibiotics (ceftriaxone and vancomycin).

Nasopharyngeal swab for SARS-CoV-2 PCR was sent, and the patient was placed in an isolation room. On the second day of admission, the patient's condition improved with resolution of respiratory symptoms and normalization of oxygen saturation (97% oxygen saturation on ambient air). Cardiology was consulted on the second day of admission. The patient underwent echocardiography that showed normal cardiac structure and function

without evidence of pulmonary hypertension or pulmonary artery anomalies. On the third day of admission, the SARS-CoV-2 PCR result returned negative, and the chest x-ray revealed complete resolution of opacities (Fig 2b). The patient was discharged home with diagnosis of re-entry HAPE given the clinical symptoms, history of travelling from low altitude areas to high altitude areas, improving respiratory symptoms, and chest x-ray abnormalities on oxygen support. Informed consent was taken from patient and patient's parents.

Patient 3

An 11-year-old boy, twin B, (sibling of patient 2) from the city of Abha (specifically AlSouda 3,015 m above sea level) presented with a one-day history of progressive dyspnea and productive cough, two days after returning from the town of Jizan (sea level) to Abha. The family spent their winter vacation (three weeks) in the Jizan area. Before traveling back to Abha, the mother reported a history of respiratory infection in all family members, but there was no history of contact with confirmed or suspected COVID-19 patients. His vital signs on admission to the emergency unit were a heart rate of 145 bpm, respiratory rate of 28 breaths/min, blood pressure of 110/ 65 mmHg, temperature of 36.5°C, and SpO₂ of 63% on RA. The lung examination revealed mild respiratory distress with crackles most commonly heard at

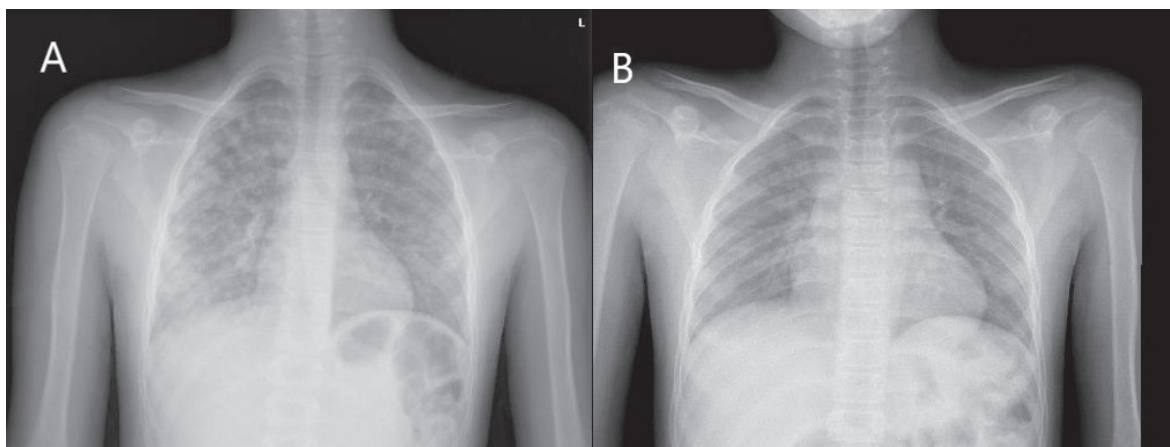


Fig. 2. Chest x-ray upon admission (A) and prior to discharge (B) for Patient 2.

lung bases. The throat examination revealed an oropharyngeal erythema without tonsillar inflammation. Neurologically, the patient was fully awake with a Glasgow coma scale of 15/15. Laboratory tests are summarized in Table I. Chest x-ray revealed bilateral heterogeneous opacities that involved both lung fields (Fig 3a). He was admitted to the general pediatric ward with suspected COVID-19 pneumonia. The patient was placed on 4 liters of oxygen through a nasal cannula and started on broad-spectrum antibiotics (ceftriaxone and vancomycin).

Nasopharyngeal swab for SARS-CoV-2 PCR was sent, and the patient was placed in the isolation room. On the second day of admission, the patient's condition improved with resolution of respiratory symptoms and normalization of oxygen saturation (97% oxygen saturation on ambient air). Cardiology was consulted on the second day of admission. The patient underwent echocardiography that showed normal cardiac structure and function without evidence of pulmonary hypertension or pulmonary artery anomalies. On the third day of admission, the SARS-CoV-2 PCR result returned negative, and the chest x-ray revealed complete resolution of opacities (Fig 3b). The patient was discharged home with diagnosis of re-entry HAPE given the clinical symptoms, history of traveling from low altitude area to high altitude area, improving respiratory symptoms, and chest x-ray abnormalities on

oxygen support. Informed consent was taken from patient and patient's parents.

Discussion

The exact pathophysiological mechanisms of HAPE are unknown. However, several studies have proposed mechanisms such as dysfunctioning voltage-dependent potassium channel and calcium channel due to non-homogenous pulmonary circulation constrictions.¹¹ Further, decreased nitric oxide synthesis plays a crucial role in HAPE manifestations.¹² Exaggeration of hypoxic pulmonary vasoconstrictions from the mechanisms mentioned above lead to pulmonary hypertension and increased capillary permeability in genetically susceptible individuals.^{3,4,6,13} An increase in inflammatory markers, interleukins, and tumor necrosis factors were also reported in several cases, which indicate possible role of viral-induced inflammation in capillary permeability.^{12,14} All patients reported mild upper respiratory infection before their illnesses, which are the likely predisposing factor for HAPE diagnosis. Several studies have correlated HAPE prevalence with concurrent respiratory infections, specifically re-entry HAPE and HARPE.^{2,9,15} The exact mechanism of upper respiratory tracts (URT) predisposing to HAPE is unknown; however, increased vascular permeability and priming the pulmonary

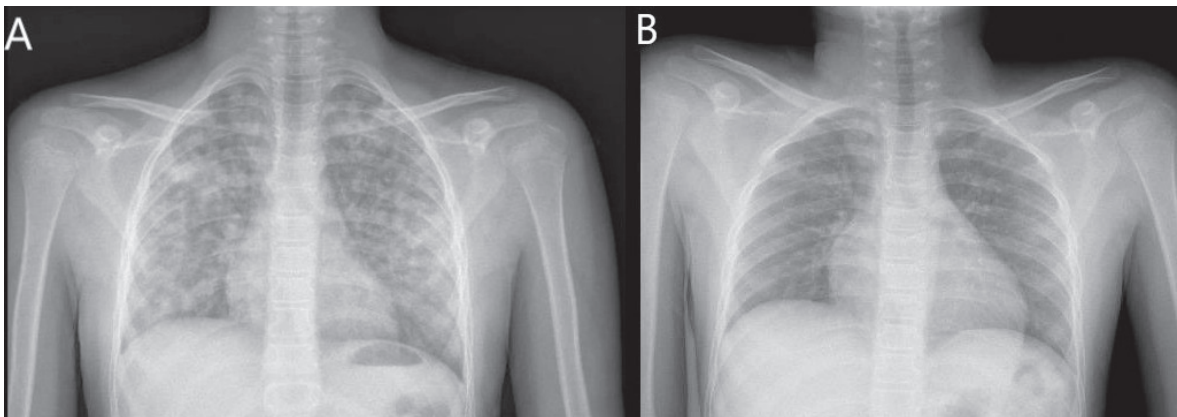


Fig. 3. Chest x-ray upon admission (A) and prior to discharge (B) for Patient 3.

capillaries for fluid leaking are the proposed pathological mechanisms.^{2-4,16,17}

Our patients were misdiagnosed with severe asthma exacerbation vs pneumonia despite the absence of typical symptoms and signs of the two illnesses, which is likely due to the lack of awareness about the diagnosis of HAPE, especially re-entry type. Rapid improvement of our patients' clinical condition and resolution of radiographic changes support the diagnosis of reentry HAPE. Based on a published pediatric HAPE case series, more than two thirds of patients received antibiotics and around half of them were misdiagnosed with pneumonia.⁹

Most of the reported pediatric case series of reentry HAPE have male predominance (Table II). Patients 2 and 3 are males and have other three female siblings who have never had any HAPE episodes. The sex difference was observed in most of the published case series and reports, suggesting that sex hormones play a role in HAPE susceptibility. Male sex hormones could predispose patients to HAPE, or that female sex hormones are protective.^{9,15,16} Further prospective and genetic studies with detailed phenotyping of HAPE patients are needed to investigate this finding.

Patient 1 reported chronic symptoms of obstructive sleep apnea with high scoring on the SRBD scale (15 out of 22) almost a year prior to her HAPE illnesses. Further, her body mass index was more than the normal age. These factors cause susceptibility to pulmonary hypertension and restrictive lung physiology with low functional residual capacity, respectively, and could explain HAPE development (patient 1) at moderate altitude (2200m).

Due to the low prevalence of this condition and the absence of randomized clinical trials to guide the treatment, management differs significantly between centers with overuse of antibiotics, steroids, and diuretics. HAPE is mostly misdiagnosed as asthma and pneumonia, which lead to overuse of the medications mentioned above.^{9,15,17} Rapid descent and supplemental

Table II. Clinical characteristic of children reported with reentry high altitude pulmonary edema.

References	Number of Patients	Age (Y)/ Gender (male-female)	History of URTs	Altitude	Treatment	Hospital stays	Outcome
Merino-Luna A et. al. ¹⁵	1	4/M	+	3052 m	Oxygen- dexamethasone- IV antibiotics	Three days	Recovered
Douglas Lopez de Guimaraes. ¹⁶	1	17/M	-	3100 m	Oxygen	Three days	Recovered
Saiki ¹⁷	1	10/M	+	3400 m	Oxygen intravenous dexamethasone, oral acetazolamide	Four days	Recovered
Baniya et. al. ²⁰	1	7/M	+	3500 m	Oxygen intravenous dexamethasone	One day	Recovered
Viruez-Soto et. al. ²¹	1	14/M	-	4090 m	Oxygen Mechanical ventilation Dexamethasone acetazolamide Sildenafil Vitamin C	Five days	Recovered
Giesenhagen et al. ⁹	19 (single center experience)	Median and range 10.2 [0.6-19.2]/ male 70% (all HAPE specified)	Not	2798 m [1840-3536]	Dexamethasone Acetazolamide antibiotics	Median duration 2.2 days for all HAPE	Recovered

oxygen are the primary treatment of HAPE. Targeting saturation level of 93% and above is recommended to relieve the pulmonary vasoconstrictions and improve hypoxemia. A nasal cannula/ face mask is the common oxygen delivering device, and rarely mechanical ventilation is necessary. Pharmacological interventions are also recommended if rapid descent is not possible, or the patients are severely distressed with more oxygen requirements. Direct pulmonary vasodilators are the main therapies used. Nifedipine has been recommended in children, especially for those who do not improve after oxygen therapy and descent.^{1,4,8} Furosemide is not recommended since it decreases the pulmonary circulation and worsens the hypoxemia as most patients present with low intravascular volume.⁴

Patients 2 and 3 presented at the time of the COVID-19 pandemic, and they were suspected to having complicated COVID-19 pneumonia despite the absence of contact with COVID-19 patients. Nasopharyngeal swabs for SARS-CoV-2 were sent and returned negative on the third day. Response to therapies and pathophysiology of HAPE and COVID-19 differ significantly.¹⁸ Development of Pulmonary edema in HAPE is due to exaggerated hypoxic pulmonary vasoconstriction while in COVID-19 the lung injury is due to an intense host cytokine-mediated inflammatory response that eventually leads to capillary permeability and surfactant dysfunction.¹⁹

In conclusion, these are the first reported cases of children with re-entry HAPE in Saudi Arabia. Re-entry HAPE can occur in otherwise healthy children, with the rapid ascent to high altitude and recent respiratory infections being the commonly reported triggers. Prognosis is favorable with a very rapid response to oxygen therapy. Education about HAPE is mandatory for families and health care workers working in high altitude areas.

Author contribution

The authors confirm contribution to the paper as follows: designed the research and drafted the manuscript: AAA, İAA; interpreted the data: AAA, HHA, AMA; performed the literature search and scientific overview of our case: AAA, WİA. All authors critically read and reviewed the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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