Pulmonary Edema in 6 Children With Down Syndrome During Travel to Moderate Altitudes
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ABSTRACT. Objective. Children with Down syndrome (DS) are living longer and are increasingly participating in recreational activities. When a child with DS was diagnosed with high-altitude pulmonary edema (HAPE), this study was undertaken to determine whether and under what circumstances children with DS develop HAPE.

Design. A retrospective review of the medical records of Children’s Hospital, Denver, Colorado was performed for children with a discharge diagnosis of HAPE. Diagnostic criteria for HAPE included the presence of crackles or frothy sputum production on examination, hypoxemia, chest radiograph findings consistent with pulmonary edema, and rapid clinical improvement after descent or oxygen therapy.

Results. A total of 52 patients with HAPE were found of whom 6 also had DS. The age range of the children with DS was 2 to 14 years. HAPE developed at altitudes ranging from 1738 to 3252 m. Four children developed HAPE within 24 hours of arrival to altitude. Three children had chronic pulmonary hypertension, and 4 had either an existing cardiac defect with left-to-right shunting or previously had a defect with left-to-right shunt that had been repaired. One child had Eisenmenger syndrome with chronic right-to-left shunting of blood. Five children had preexisting illnesses before travel to altitude.

Conclusion. Children with DS often have medical problems such as chronic pulmonary hypertension, frequent infections, and pulmonary vascular overperfusion and injury from existing or previous cardiac defects. These problems all may be viewed as risk factors for HAPE and thus result in the rapid development of HAPE at low altitudes. Care should be taken when traveling to even moderate altitudes with children with DS.

Materials and Methods

The medical records of children with a discharge diagnosis of HAPE or other altitude related illness were identified from the medical record database of the Children’s Hospital in Denver, Colorado. A total of 52 children with HAPE were found of whom 6 also had DS. HAPE was diagnosed by the attending physician at the referring clinic or Children’s Hospital. Diagnostic criteria included the presence of hypoxemia as determined by cyanosis and low oxygen saturation or partial pressure of arterial blood oxygen, presence of crackles or frothy sputum on examination, a chest radiograph film consistent with pulmonary edema, and rapid clinical improvement after institution of oxygen therapy or decrease in terrestrial elevation. Because of the high incidence of congenital heart defects in children with DS, cases presented included an evaluation of cardiac function by echocardiogram, electrocardiogram, or a cardiologist’s clinical consultation. In addition, charts were analyzed for age, sex, temperature, altitude reached, and duration of altitude exposure. Because studies show that the presence of a mild respiratory infection before or during travel to altitude may predispose to HAPE, historical and clinical data were also examined for evidence of recent signs and symptoms of infection.

Patient 1

This child was a 14-year-old girl with DS who arrived in Glenwood Springs, Colorado (elevation 1738 m) from Houston, Texas 4 days before admission. The child had a patent ductus arteriosus (PDA) ligated in the first year of life. She had been to high elevations previously without problems. Two days after arrival she developed a progressively worsening cough and cyanosis and sought medical attention in Glenwood Springs. In the week before the present admission she had had diarrhea and symptoms of an upper respiratory tract infection (URI). In Glen-
wood Springs she was noted to be afebrile, tachypneic, and very obese (110 kg). Bilateral crackles were noted on lung examination. The cardiac examination was normal. Oxygen saturation was 53% while breathing room air (expected normal 93%). Oxygen was administered and the child transferred to Children’s Hospital. At Children’s Hospital, oxygen saturation was 95% while breathing 3 L/min oxygen by nasal cannula. A chest radiograph revealed pulmonary vascular congestion with pulmonary edema (Fig 1A). An echocardiogram demonstrated normal cardiac anatomy with good cardiac function. Specifically, right ventricular size and function were normal. No significant tricuspid regurgitation was noted. She was treated with oxygen and rest, with resolution of symptoms and radiographic improvement within 24 hours (Fig 1B).

Patient 2

This child was a 3-year-old boy with DS who developed lethargy, fever, respiratory distress, and apnea in Summit County (elevation 2744 m) while traveling by automobile across Colorado. He had been exposed to altitudes of 2134 to 3049 m for approximately 1 day. The child had been prescribed eye drops to treat conjunctivitis in Los Angeles, California 3 to 4 days before presentation. At Summit County Medical Center, the child had a cough and was tachypneic. Oxygen saturation was noted to be 54% while breathing room air (expected normal 91%). The child was transported to Children’s Hospital, where the pulse was 120, respiratory rate 32, blood pressure 96/45 mm Hg, and temperature 39°C. Ear examination revealed an inflamed left tympanic membrane. Pulmonary examination revealed a cough and coarse breath sounds bilaterally. Cardiac examination revealed a 3/6 pansystolic murmur. Laboratory studies showed a white blood cell count of 12 600 mm$^{-3}$ with 63% neutrophils and a hemoglobin of 12.3 g/dL. Oxygen saturation was 96% while breathing oxygen at 1 L/min via nasal cannula. A chest radiograph revealed increased pulmonary vascularity with pulmonary edema (Fig 2A). An echocardiogram demonstrated normal intracardiac anatomy and function. Right ventricular hypertrophy was present. Flow in the pulmonary artery and descending aorta was suggestive of a small PDA. The child was treated with oxygen and antibiotics. Clinical symptoms improved rapidly. Another chest radiograph less than 24 hours after admission showed significant resolution of pulmonary edema (Fig 2B).

Patient 3

This child was a 3-year-old boy with DS who presented with lethargy, cough, tachypnea, and cyanosis 1 day after arrival to Colorado from Houston, Texas. Otitis media was diagnosed 9 days before arrival in Colorado and was treated with antibiotics. There was no history of cardiac or respiratory diseases. The day of admission the child was taken to Loveland Ski Resort (altitude 3049 m). The child developed tachypnea and cough and became increasingly lethargic. The mother noted perioral cyanosis and took the child to the emergency medical facility at the mountain, where his oxygen saturation determined by pulse oximetry was 50% (expected normal 89%–90%). Supplemental oxygen was given and the child transported to Children’s Hospital by ground ambulance. On arrival determination of vital signs revealed a pulse of 124, respiratory rate 40, blood pressure 116/54, and temperature 37.2°C. Pulmonary examination revealed fine crackles bilaterally but most prominently at the left lung base. Mild expiratory wheezes were also heard. Cardiac examination was normal except for tachycardia. The oxygen saturation was 83% while breathing room air and increased to 92% with 1 L/min of oxygen via nasal cannula. A chest radiograph revealed bilateral fluffy infiltrates consistent with pulmonary edema. The child was treated with antibiotics, albuterol by nebulization, and oxygen by nasal cannula. His clinical condition improved dramatically within 12 hours, with discharge from the hospital after 1 day.

Patient 4

This child was a 6-year-old girl with DS who developed respiratory distress, cough productive of frothy pink fluid, and cyanosis while traveling over Vail Pass (elevation 3252 m) by automo-
The duration of exposure to altitude greater than 2134 m was approximately 1 day. The child had a history of a “hole in the heart” that, after cardiac catheterization 3 years before, the family was told was inoperable. The child had traveled through Colorado previously by routes lower in altitude. At Summit County Medical Center in Frisco, Colorado, she was cyanotic with a respiratory rate of 52. Oxygen was administered and the child transported to Children’s Hospital, where physical examination showed a pulse of 104, respiratory rate of 28, blood pressure of 86/70 mm Hg, and temperature of 37.5°C. Lung examination revealed scattered crackles bilaterally. Cardiac examination showed a 1/6 systolic murmur, prominent second heart sound, and palpable pulmonary valve closure. There was clubbing of the digits. No peripheral edema was noted. Laboratory studies showed a white blood cell count of 12 100 μm³ and hematocrit of 40%. Chest radiograph revealed bilateral pulmonary edema. An arterial blood gas while breathing supplemental oxygen at Children’s Hospital (1610 m) revealed a pH of 7.37, PCO₂ 39 torr, PO₂ 32 torr, and HCO₃ 22. A repeat blood gas the next day continued to demonstrate profound hypoxemia, with a PO₂ of 32 torr. A cardiology consultation and discussion with the child’s physician in California confirmed the presence of a ventricular septal defect (VSD), PDA, and severe pulmonary hypertension with right-to-left shunting of blood that was not responsive to oxygen. An echocardiogram demonstrated normal left ventricular size and function (diastolic diameter 4.14 cm, systolic diameter 2.10 cm, and ejection fraction of 0.87). The left atrium was not enlarged. The child was treated with oxygen and furosemide. She improved clinically over several days, and supplemental oxygen was progressively decreased. She continued to have perioral cyanosis, which the family said was normal for her. After 3 days of hospitalization, the family returned to California by a route of lesser altitude.

**Patient 5**

This child was a 4-year-old boy with DS who presented in Breckenridge, Colorado (elevation 2744 m) with tachypnea and cyanosis the day of arrival from Little Rock, Arkansas. The child had been hospitalized in Little Rock as a result of an exacerbation of asthma and was discharged a week before traveling to Colorado. The child had a previous atrial septal defect (ASD) repaired at 18 months of age. There was a history of previous travel to 2134 m altitude without problems. At Summit County Medical Center the child was restless and had perioral and central cyanosis. Oxygen was administered and the child transported to Children’s Hospital for additional evaluation. The transport team noted that his clinical status improved dramatically during the transport to Denver. At Children’s Hospital, physical examination revealed a pulse of 140, respiratory rate of 56, blood pressure of 80/66 mm Hg, and temperature of 38.9°C. Lung examination demonstrated diffuse bilateral crackles without wheezes; the cardiac examination was normal. An ASD was evident. A chest radiograph revealed diffuse pulmonary edema (Fig 3A). An echocardiogram demonstrated evidence of pulmonary hypertension. The child was treated with oxygen, aminophylline, and glucocorticoids. He improved both clinically and radiographically within 24 hours (Fig 3B). Maintenance therapy of oral theophylline, which had been prescribed at home, was continued. He returned home 3 days later.

**Patient 6**

This child was a 2-year-old girl with DS who presented with sleeplessness and cough and for 3 days since the family arrived in Summit County, Colorado (elevation 2744 m) from Missouri. History included bronchitis and otitis media, for which 10 days of antibiotic therapy had just been completed. In addition, the parents reported the child as having an unrepaired ASD and VSD. At Summit County Medical Center, the pulse was 160, respiratory rate 36, and temperature 37.6°C. Crackles were heard at the lung bases bilaterally. Oxygen saturation by pulse oximetry was 68% (expected normal 91%) while breathing room air, which improved to 91% with 5 L/min flow of oxygen by face mask. Albuterol was given via small volume nebulizer. The child was transferred to Children’s Hospital, where the pulse was 136, respiratory rate 32, and temperature 36.5°C. Breath sounds were described as coarse bilaterally with rhonchi. The cardiac examination showed a 3/6 holosystolic murmur. Laboratory investigation showed a white blood cell count of 12 600 μm³ with 56% neutrophils and a hemoglobin of 14.1 g/dL. A chest radiograph demonstrated normal heart size and fluffy pulmonary infiltrates bilaterally consistent with pulmonary edema. An electrocardiogram demonstrated right axis deviation and right ventricular hypertrophy. An echocardiogram showed flattening of the interventricular septum, high-velocity left-to-right blood flow across a small break in the interventricular septum, and good cardiac function. An ASD was not visualized. The child was treated initially with 2 L/min oxygen by nasal cannula and furosemide. Antibiotics were begun for possible pneumonia. She improved rapidly and returned to Missouri 3 days after presentation.

**DISCUSSION**

Six children with DS developed pulmonary edema at the moderate elevations (altitude 1734–3252 m) found in the resort areas and towns west of Denver, Colorado (data summarized in Table 1). All children had good cardiac function on cardiac evaluation, thus helping to confirm that the pulmonary edema was not the result of left ventricular failure. These cases are unique because of the low altitude and brief exposure to altitude that precipitated HAPE. This
suggests that children with DS may be at higher risk for the rapid development of HAPE at low altitudes.

Increased pulmonary vasoreactivity and pulmonary hypertension are prerequisites for HAPE, and treatment of or prophylaxis against pulmonary hypertension with vasodilators hastens clinical resolution or prevents HAPE. Those with DS are at higher risk for developing pulmonary hypertension. They have greater pulmonary vascular reactivity and develop greater degrees of pulmonary hypertension in the presence of increased pulmonary blood flow than normal children. In addition, the presence of a congenital heart defect resulting in increased pulmonary blood flow, as found in patients 2 and 6, may increase pulmonary artery pressure even before exposure to the hypoxia of altitude. Individuals with DS have smaller lungs than the normal population. The smaller cross-sectional area of the pulmonary vascular bed also could place them at greater risk for HAPE similar to the greater risk in those with an absent or hypoplastic pulmonary artery.

Patients 1 and 5 had previous congenital heart defects that had been corrected. There is evidence in both humans and animal models that the presence of even a mild inflammatory stimulus to the pulmonary vasculature, as would occur with increased pulmonary blood flow and pressure, continue to affect the lungs long after their resolution. For example, Sartori et al identified infants who had significant pulmonary hypertension at birth that was treated with mechanical ventilation and oxygen. An average of 21 years later, they reassessed pulmonary artery pressure and reactivity at altitude in this group compared with a control group with normal neonatal periods. Although their baseline pulmonary pressures were normal, the pulmonary hypertension group had significantly higher pulmonary artery reactivity and pressure at high altitude than the control group. These findings suggest the pulmonary vasculature, once injured, may be more sensitive to potentially pathologic stimuli such as hypoxia, even years after the initial insult. Thus, although their heart defects had been repaired, patients 1 and 5 may still be at risk for the rapid development of pulmonary hypertension and subsequent risk for HAPE even at modest elevations.

Patients 1, 2, 3, 5, and 6 all had a preceding or concurrent illness such as a URI (Table 1). It has been demonstrated both in humans and experimental animals that the presence of even a mild inflammatory illness such as a URI may be a risk factor for the development of HAPE in children. Intercurrent illness may play an even greater role in the development of HAPE in children with DS because their impaired immune system results in a greater number and severity of infections.

Another manifestation of DS that may be viewed as a risk factor for HAPE is the high incidence of obstructive apnea and hypoventilation, resulting in both hypoxia and hypercarbia. Otherwise normal individuals susceptible to HAPE have relative hypovolaemia at altitude, resulting in more severe hypoxia and relative hypercarbia. In this case report the presence of DS and obesity placed patient 1 at high risk for apnea and hypoventilation. Hypoventilation at altitude would result in more severe hypoxia, which would increase pulmonary vasoconstriction, hypertension, and risk of HAPE. Indeed, in this child the constellation of risk factors including DS, abnormal pulmonary circulation in infancy, previous infection, and obesity with possible hypovolaemia could be hypothesized as the reason this child developed HAPE at one of the lowest reported altitudes (1738 m).

Patient 4, who had severe pulmonary hypertension with right to left shunting of blood is believed to be the first reported patient with HAPE in the presence of decreased total pulmonary blood flow. Experimental evidence supports several theories that could explain the development of pulmonary edema under conditions of high pressure but low total pulmonary blood flow. Whayne and Severinghaus presented evidence in experimental animals that extravasation of edema fluid from precapillary pulmonary arterioles may occur under conditions of high pressure. Another theory is based on evidence that structural remodeling from pulmonary hypertension is not uniform. Although some small pulmonary arteries are nearly obliterated, other precapillary vessels are dilated and have thin walls. Thus, despite decreased total pulmonary blood flow, the uneven remodeling could result in localized high flow and pressure in the patent, dilated vessels with resultant edema formation. In addition, Maggiorini et al recently provided evidence in humans that suggests that active pulmonary postcapillary venoconstriction may contribute to the development of pulmonary edema in HAPE. This would result in increased pulmonary capillary pressure and probably edema despite high precapillary resistance. Thus, it is possible that transarteriolar leak, localized overperfusion, or venoconstriction and could be responsible for the rapid development of pulmonary hypertension and subse-

### Table 1. Summary of Patient Data

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age</th>
<th>Altitude of Illness</th>
<th>Duration at Altitude</th>
<th>Active Left to Right Shunt</th>
<th>Chronic Pulmonary Hypertension</th>
<th>Abnormal Pulmonary Circulation in Infancy</th>
<th>Preceding/Concurrent Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14 y</td>
<td>1738 m</td>
<td>4 d</td>
<td>No</td>
<td>No</td>
<td>Yes (PDA)</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>3 y</td>
<td>2744 m</td>
<td>&lt;1 d</td>
<td>Yes (PDA)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>3 y</td>
<td>3049 m</td>
<td>&lt;1 d</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>6 y</td>
<td>3252 m</td>
<td>&lt;1 d</td>
<td>No</td>
<td>Yes*</td>
<td>Yes (VSD, PDA)</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>4 y</td>
<td>2744 m</td>
<td>1 d</td>
<td>No</td>
<td>No</td>
<td>Yes (ASD)</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>2 y</td>
<td>2744 m</td>
<td>3 d</td>
<td>Yes (VSD)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Severe chronic pulmonary hypertension with right to left shunting of blood.
for edema formation in this patient with Eisenmenger syndrome who developed HAPE.

CONCLUSION

The cases presented here describe the rapid development of pulmonary edema at moderate altitudes in children with DS, including a case of HAPE in a child with Eisenmenger syndrome. We do not believe that this is a set of repeated, rare coincidences; rather, children with DS have features that increase their risk of HAPE. Indeed, the cardiac and pulmonary problems inherent in DS share physiologic features with risk factors that predispose otherwise normal individuals to HAPE. The features include increased pulmonary reactivity, presence of pulmonary hypertension, lung hypoplasia, increased pulmonary blood flow caused by congenital heart disease, and a susceptibility to apnea and hypventilation. These features, together with other known risk factors such as rapid ascent and infection, set the stage for HAPE. Lack of reports to date may result from the scarcity of both DS and HAPE or the lack of travel of those with DS to altitude. The cases presented also raise theoretical questions about the pathogenesis of HAPE, as in the child with Eisenmenger syndrome, and questions about the safety of children with DS traveling to altitude, especially those with a potentially abnormal pulmonary circulation. Much more research is needed to determine the physiologic responses of those with DS to altitude. Because such data are lacking and children with DS more fully participate in recreational activities, including those at altitude, it is appropriate to counsel families of children with DS about possible increased risks of travel to and recreation at even moderate altitudes.

REFERENCES

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