Pulmonary Hypertension Associated With Scurvy and Vitamin Deficiencies in an Autistic Child

abstract

Restricted dietary intake is common among children with behavioral issues. Here we report a case of a severely autistic child who presented initially with limp but who soon developed cough, tachypnea, hypoxia, and tachycardia. An echocardiogram revealed evidence of pulmonary hypertension (PH) with severely dilated right ventricle and elevated right-sided pressures. The etiology of his PH was unclear but further laboratory evaluation demonstrated severe nutritional deficiencies, in particular an undetectable ascorbic acid (vitamin C) level as well as deficient levels of thiamine (vitamin B1), pyridoxine (vitamin B6), cobalamin (vitamin B12), and vitamin D. Repletion of these vitamins was associated with resolution of his PH and his musculoskeletal complaints. We report this case and a review of the relevant literature as a clinical lesson to expand the differential diagnosis of limp in children who may be difficult to assess as well as to report on an unusual association between severe vitamin deficiencies and PH. Pediatrics 2013;132:e1699–e1703
Pulmonary hypertension (PH) is characterized by elevated blood pressures in the pulmonary circulation and can lead to right heart disease. Known etiologies of PH include diseases that affect the pulmonary vasculature directly, thromboembolic disease, left-sided and congenital heart disease, or lung disease and hypoxemia. To our knowledge, vitamin and mineral deficiencies have only rarely been reported in association with PH in the human literature. We report a case of restrictive eating and ensuing development of scurvy and other vitamin deficiencies in an autistic child who subsequently developed PH.

**PATIENT PRESENTATION/CASE REPORT**

The patient is a 9-year-old boy with autism spectrum disorder who developed a limp 4 months before presentation. Neurologic and orthopedic evaluations did not reveal an etiology for the limp and the patient’s symptoms worsened despite physical therapy. The patient was taken to the emergency department (ED) where bilateral hip and knee films were normal and complete blood count and inflammatory markers were reassuring. The patient was discharged and received outpatient MRI, which showed focal bone marrow T2 hyperintensity and enhancement of the metaphyseal equivalents of the pelvis and proximal femoral apophyses, concerning for spondyloarthopathy or metabolic bone disease. The patient’s symptoms continued to worsen until he was entirely unable to ambulate, and he returned to the ED 3 weeks later. By this time, he was unable to ambulate, and he returned to the general pediatrics department (ED) where bilateral hip and knee radiographs showed diffuse, nodular, ill-defined airspace opacities throughout the right lung greater than left lung (consistent with cardiogenic pulmonary edema versus pneumonia) and small right pleural effusion and an enlarged main pulmonary artery (Fig 1). An electrocardiogram was obtained and showed sinus tachycardia with a left axis deviation, and right heart strain pattern with incomplete right bundle branch block, and nonspecific ST and T-wave changes. A bedside echocardiogram was obtained and showed a severely dilated right ventricle (RV) with mild to moderately depressed systolic function and a dilated right atrium and pulmonary artery (Fig 2A). RV pressures determined by peak pulmonary regurgitant jet velocity showed systolic pressure as high as 65 to 70 mm Hg plus the right atrial v-wave (reference range: <36 mm Hg), mean pulmonary artery pressure of 45 mm Hg (reference range: <25 mm Hg), and end-diastolic pressure of 30 mm Hg plus the right atrial pressure (not wave) (reference range: 8–10 mm Hg; Fig 3) determined from the pulmonary regurgitant velocities.

Workup of his PH included a computed tomography angiogram, which showed normal pulmonary veins, a dilated main pulmonary artery, and mild to moderately depressed systolic function with mild right ventricular enlargement.

**TABLE 1** Initial Laboratory Evaluation on Presentation to the ED

<table>
<thead>
<tr>
<th>Laboratory Study</th>
<th>Level</th>
<th>Normal Range</th>
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</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>$6.21 \times 10^3/\text{mm}^3$</td>
<td>5.7–9.9 $\times 10^3/\text{mm}^3$</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>34.40%</td>
<td>31.5%–38.0%</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>82.3 $\times 10^3/\text{mm}^3$</td>
<td>198–371 $\times 10^3/\text{mm}^3$</td>
</tr>
<tr>
<td>Platelets</td>
<td>$625 \times 10^3/\text{mm}^3$</td>
<td>111–198 $\times 10^3/\text{mm}^3$</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>23 mm/h</td>
<td>20–30 mm/h</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.13 mg/dL</td>
<td>≤0.5 mg/dL</td>
</tr>
<tr>
<td>Sodium</td>
<td>130 mmol/L</td>
<td>135–148 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.32 mmol/L</td>
<td>3.2–4.5 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>93 mmol/L</td>
<td>99–111 mmol/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>12 mmol/L</td>
<td>22–30 mmol/L</td>
</tr>
<tr>
<td>Serum urea nitrogen</td>
<td>18 mg/dL</td>
<td>5–18 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.5 mg/dL</td>
<td>0.3–0.7 mg/dL</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.7 mg/dL</td>
<td>8.0–10.5 mg/dL</td>
</tr>
<tr>
<td>Ionized calcium</td>
<td>1.14 mmol/L</td>
<td>1.14–1.29 mmol/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>74 mg/dL</td>
<td>61–100 mg/dL</td>
</tr>
<tr>
<td>Anion gap</td>
<td>25 mmol/L</td>
<td>7–14 mmol/L</td>
</tr>
<tr>
<td>B-natriuretic peptide</td>
<td>2091 pg/mL</td>
<td>&lt;100 pg/mL</td>
</tr>
</tbody>
</table>
pulmonary artery (3.2 cm), and no filling defect to suggest pulmonary embolus. Lower extremity Doppler ultrasounds were negative for deep vein thrombosis. Hypercoagulable workup was normal. Despite diuresis over the course of hospital day (HD) 2 through 5 and treatment of presumed pneumonia, serial echocardiograms on HDs 2, 3, and 4 showed persistent severe elevation of RV pressure as well as severely dilated RV with moderate dysfunction. The patient remained tachypneic despite diuresis, adequate antibiotics for possible pneumonia, and supplemental oxygen therapy.

A dietary history revealed that for the past 3 years the child had eaten a diet consisting mainly of white foods, including chicken nuggets, crackers, cookies, and water. He refused milk, juice, vegetables, and fruits and was not on vitamin supplementation. Assays for vitamin and mineral levels revealed an undetectable level of vitamin C as well as deficiencies in vitamins B1, B6, and D (Table 2). Parathyroid hormone function was attenuated at 4.4 pg/mL (normal 10–65 pg/mL). Vitamin A, vitamin B2, vitamin B5, vitamin E, selenium, zinc, and folate levels were all within normal limits. His vitamin deficiencies were repleted over the course of HD 6 through HD 14 with intravenous ascorbic acid, thiamine, ergocalciferol, and a multivitamin preparation as well as intramuscular vitamin B12 injections.

By HD 11, after repletion of water-soluble vitamins, his respiratory rate had decreased to the normal range. By HD 15, a repeat echocardiogram showed RV pressure less than half systemic pressure by septal position and resolution of RV dilation and normal systolic function (Fig 2B). He was discharged from the hospital after 3 weeks to continue oral supplementation with a multivitamin preparation as well as calcium and ergocalciferol. By HD 11, after repletion of water-soluble vitamins, his respiratory rate had decreased to the normal range. By HD 15, a repeat echocardiogram showed RV pressure less than half systemic pressure by septal position and resolution of RV dilation and normal systolic function (Fig 2B). He was discharged from the hospital after 3 weeks to continue oral supplementation with a multivitamin preparation as well as calcium and ergocalciferol. At the time of discharge, he was able to ambulate with assistance without pain. Over the past 18 months, vitamin levels have remained normal on vitamin supplements, and repeat echocardiograms have shown normal RV pressures and function.

DISCUSSION

We report an unusual case of severe vitamin malnutrition associated with limp and refusal to bear weight as well as PH with reversible right heart failure. We initially considered pneumonia as a possible etiology for the observed PH, as the chest radiograph demonstrated bilateral nodular infiltrates. However, no infectious etiology was elucidated and after adequate diuresis and treatment of possible pneumonia, chest radiograph findings and PH persisted, leading us to search for alternate explanations. Oncologic diseases were considered given MRI findings, but supplemental evidence did not support this diagnosis. Given the patient’s severely restricted diet, vitamin and mineral levels were sent and returned with undetectable vitamin C level, as well as inadequate levels of vitamin B1, B6, B12, and D as reported previously. Thiamine (vitamin B1) deficiency resulting in “cardiovascular beriberi” has been reported as a rare reversible cause of PH and cor pulmonale and is generally characterized by high-output right-sided heart failure and rarely cardiovascular collapse (Shoshin beriberi). Case reports of thiamine deficiency associated with PH are primarily in the setting of inadequate intake of thiamine-containing foods and alcoholism. A recent study in India investigated 55 breastfeeding infants of low socioeconomic status who presented with signs of right heart failure with tachypnea, increased work of breathing, and tachycardia and most had dilated right heart and PH. Most of these infants were deficient in thiamine and repletion of vitamin B1 led to resolution of their heart failure symptoms.

To our knowledge, there have been no case reports of pediatric patients with scurvy presenting with PH, although 2
adult patients have been described in case reports to have this association.\textsuperscript{6,7} In an animal model of PH, supplemental vitamin C reduced PH and the associated muscularization of pulmonary arterioles that is caused by their exposure to cool environmental temperatures.\textsuperscript{8}

Nitric oxide (NO) is a potent mediator of vascular smooth muscle relaxation and is generated by the conversion of L-arginine to L-citrulline by the enzymatic action of NO synthetase. Ascorbic acid has been shown to increase the production of NO by endothelial cells by promoting the degradation of the NO synthetase inhibitor asymmetric dimethyl L-arginine, stabilizing and increasing NO synthetase cofactors, and inhibiting the arginase pathway that competes for arginine.\textsuperscript{9} We postulate that in a patient with undetectable levels of ascorbic acid, the NO pathway could be compromised, leading to insufficient NO production and a state of increased vascular tone resulting in PH.

Vitamin C is also an essential cofactor for the family of prolyl hydroxylases that serve as oxygen sensors and regulate the activity of the hypoxia-inducible family of transcription factors, the major controller of the body’s response to hypoxia. In the setting of vitamin C deficiency, unregulated hypoxia-inducible family activity may trigger an inappropriate response to hypoxia, leading to deleterious pulmonary vasoconstriction and PH.\textsuperscript{10}

Finally, recent reports have linked disruption in the scavenging of reactive oxygen species to the progression and pathology of PH.\textsuperscript{11,12} As an antioxidant, vitamin C may have multiple beneficial effects in scavenging reactive oxygen species and preventing downstream pulmonary vasoconstriction.

Our patient’s limp and bleeding gums were likely a result of vitamin C deficiency and the MRI findings could be explained by subperiosteal hemorrhages secondary to collagen synthesis defects.\textsuperscript{13} Although it is difficult to attribute causality in this case, it is certainly highly correlative that on repletion of both vitamin C and other vitamins, our patient’s limp as well as his PH resolved.

**CONCLUSIONS**

We report a case of scurvy and other vitamin deficiencies associated with both metabolic bone disease and reversible PH in a child with autism. This case highlights the fact that pediatricians should be aware of the unusual symptoms with which this type of malnutrition can present, including manifestations of metabolic bone disease and symptoms of heart failure. Patients at particular risk of these severe vitamin deficiencies include not only patients with behavioral issues, such our patient, but also patients with restrictive eating disorders/anorexia, children of low socioeconomic status, immigrants and refugees, and patients with chronic diseases, such as HIV/AIDS. In addition, we suggest that nutritional deficiencies be screened for in the evaluation of PH in at-risk patients, such as those with cognitive behavioral disturbances or restricted nutritional intake.
REFERENCES

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