Cardiology in the Young

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Vitamin C deficiency as an unusual cause of pulmonary hypertension and refusal to walk

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Abstract

Vitamin C deficiency has been a historical disease rarely seen nowadays. We illustrate a case of a boy with autism presenting with severe pulmonary hypertension and refusal to walk secondary to vitamin C deficiency. Initiating treatment with high-dose vitamin C reversed his symptoms and he regained full power of his lower limbs with total normalisation of his pulmonary pressures.

Brief Report

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Vitamin C deficiency is a nutritional disease rarely seen in today's society. It is rarely thought of as a contributing factor for pulmonary hypertension. We present a case to highlight this important link.

Case report

A 7-year-old boy with underlying autistic spectrum disorder was first presented to the general paediatrician with lethargy, anorexia, and refusal to walk. He was planned for MRI brain and spine. However, after MRI brain, he developed unexplained sinus tachycardia and MRI spine was aborted.

An echocardiogram revealed a hypertensive right ventricle with a septal shift to the left and moderate tricuspid regurgitation with a peak gradient of 75 mmHg; suggesting pulmonary hypertension. With a systemic blood pressure at that time of 90/57 mmHg, his pulmonary pressure was about 75% systemic (Fig 1a, b, and c). Cardiac enzymes were mildly elevated and there were no significant ECG changes besides sinus tachycardia.

MRI brain and nerve conduction study were both normal. He underwent physiotherapy and was discharged with diuretics only to present again 2 days later with dyspnoea and right heart failure. He had bilateral ankle oedema, hepatomegaly, and was tachycardic. He failed to maintain saturations in room air and was referred to our centre for further treatment.

Upon arrival, he was noted to be lethargic and breathless. He was brought to the intensive care unit (ICU) for ventilation. CT scan of the lungs showed evidence of right heart congestion. There was no pulmonary arterial embolism or interstitial lung disease. Inhaled nitric oxide, phosphodiesterase 5 inhibitor, and endothelin-receptor antagonist were initiated but there were no signs of improvement. Investigation for conventional secondary causes of pulmonary hypertension did not yield any positive results. He progressed to multi-organ impairment in the ICU and he was not stable for a diagnostic cardiac catheterisation.

Upon further history taking, he was found to have a very limited diet of only fish and soup daily. He does not take vegetables and is very selective with his fruit intake. Prior to this illness, he had no activity limitation and would play on the trampoline daily. Suspecting that his symptoms may be nutritionally mediated, serum ascorbic acid level was sent for analysis and he was empirically started on vitamin C supplementation of 1000 mg daily. He did not exhibit any classical signs of vitamin C deficiency, such as gum bleeding or petechiae.

Over the course of 10 days, his pulmonary hypertension improved significantly (Fig 1d, e, and f). His ventilator settings were gradually weaned and he was extubated. All organ functions improved and he underwent physiotherapy. Neurology consult did not find any pathologies to suggest central or peripheral neuropathy. He was discharged home with 1000 mg of vitamin C daily. Plasma vitamin C level prior to starting treatment was confirmed to be almost undetectable (<5μmol/L). Complement levels and connective tissue screen were normal. Respiratory viruses screening and blood cultures were all negative.

During a follow-up of 3 months later, he had regained full power of lower limbs and is back to his usual activity. A follow-up diagnostic catheterisation revealed a normal mean pulmonary arterial pressure of 14 mmHg and a pulmonary vascular resistance of 1.18 Woods unit × m^2. Pulmonary hypertensive medication was stopped and he was maintained on vitamin C supplementation.

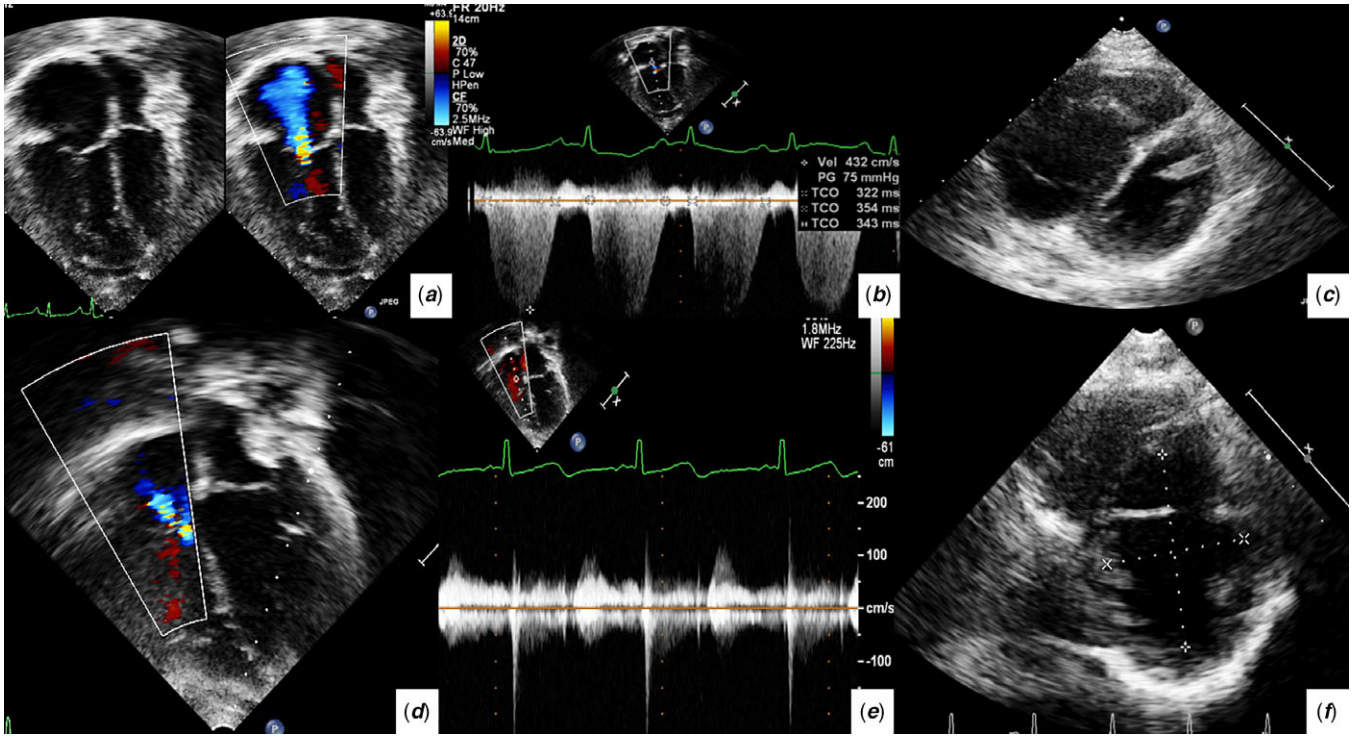

Figure 1. Pre-vitamin C therapy. (***a***) Severe tricuspid regurgitation peak and dilated right heart chambers. Note the small pericardial effusion. (***b***) Peak tricuspid regurgitant gradient 75 mmHg. (***c***) Flattening of the interventricular septum in diastole. Post-vitamin C therapy. (***d***) Trivial tricuspid regurgitation and normal right heart chamber size. (***e***) No significant peak tricuspid regurgitant gradient. (***f***) Normalisation of interventricular septum in diastole.

Discussion

Our patient presented with severe pulmonary hypertension which progressed over a period of 2 months. Dietary history revealed his lack of nutritional variety especially for fruits or vegetables and he was thus screened for vitamin C deficiency.

It is interesting to note that vitamin C deficiency may present initially with refusal to walk. In a review by Ratanachu-Ek et al, this was evident in 96% of their patients.[1] The range of differential diagnoses for refusal to walk is so broad that 86% of their patients were initially misdiagnosed. Moreover, children with behavioural disorders may not be able to describe any pain or discomfort in their lower limbs and this made the diagnosis more elusive. These children usually end up with extensive testing, some of which are invasive and costly.[2] The absence of major mucocutaneous and musculoskeletal manifestations in our patient, e.g., perifollicular petechiae, easy bruising, gum swelling, and bone disease had led to delayed diagnosis and he was referred to a cardiac centre when he developed severe, progressive pulmonary hypertension.[3,4]

It has been postulated that pulmonary hypertension in vitamin C deficiency may be attributed to three mechanisms.[5] The first mechanism involves uncontrolled Hypoxia Inducible Factor (HIF) activity. HIF is regulated by prolyl hydroxylases, which require vitamin C as a cofactor. Vitamin C depletion impedes cellular response to low-oxygen environment. The second mechanism involves the nitric oxide synthase pathway. Nitric oxide is responsible for pulmonary vascular smooth muscle relaxation. Vitamin C increases the levels of nitric oxide synthase by assisting degradation of its inhibitor, asymmetric dimethyl L-arginine. With the deficiency of vitamin C, nitric oxide levels would be low, leading to increased pulmonary vascular resistance.[6] Third, pulmonary hypertension has been linked to an excess in reactive oxygen species (ROS) activity, which would disrupt normal regulation of vascular tone.[7] Ascorbic acid is an antioxidant and severe deficiency could lead to unchecked scavenging of reactive oxygen species, which then leads to or exacerbate pulmonary hypertension.

The progression of pulmonary hypertension in vitamin C deficiency can be slow, progressing over months or rapid, leading to cardiac arrest.[8,9] Life-threatening episodes are not infrequently present during sedation or general anaesthesia for procedures.[9,10]

Conclusion

This case illustrates the importance of dietary history in managing children who present with severe, unexplained pulmonary hypertension. Notably, children with behavioural disorders, abnormal eating habits, and those who are socio-economically deprived are at higher risk for this condition. Screening for vitamin C deficiency should be included as part of the workup in at-risk children (constellation of abnormal dietary habits, muscle weakness, and pulmonary hypertension) as it is easily reversible and as illustrated in our case, life-saving.

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Conflict of interest. None.

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Ethical standards. Written informed consent has been obtained from the parents for the purpose of this publication and this is consistent with guidelines of our institutional review board.

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