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Idiopathic Pulmonary Hypertension in a Nigerian child: A case report of the clinical course and challenges of management in resource limited setting.

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Abstract
Background: *Idiopathic pulmonary hypertension (IPH) is an uncommon diagnosis in children that can lead to significant morbidity. In resource limited setting, management of affected patients can be quite challenging. We present a case of IPH in a 3-yr old girl, highlighting some of the challenges in the diagnosis and management of the patient.*
Case Report: *HR, a 3-year-old girl presented with recurrent breathlessness, cough and body swelling since the age of 3 months. She was referred for further evaluation on account of persistent symptoms despite treatment for bronchopneumonia and 2 months course of anti-tuberculous drugs.*
On echocardiogram, she had pulmonary hypertension (PH) with structurally normal heart and no other identifiable cause for the elevated pulmonary pressure. Facilities for cardiac catheterization, Cardiac CT and MRI were not available for further evaluation. She initially had good response to PH directed therapy with sildenafil and Bosentan. However, the latter drug could not be continued by the patient due to non-availability and cost; and she deteriorated gradually and died.
Conclusion: *Idiopathic pulmonary hypertension does occur in children and shows good response to dual therapy with sildenafil and Bosentan. Though echocardiography can help significantly in the evaluation of patient with IPH, facilities for right heart catheterization should be made readily available in the health care facilities of developing nations to allow for a more accurate diagnosis.*

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I. Introduction

Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure (MPAP) greater than or equals to 25 mmHg at sea level.[1,2&3] The definition is the same both in adults and children.[2,3] When there is no known identifiable cause, it is referred to as idiopathic or primary pulmonary hypertension. It can present at any age from infancy to adulthood.[3] The most common forms in children are idiopathic pulmonary hypertension and PH associated with congenital heart disease.[2,3] In children, idiopathic PH is usually diagnosed late even though patients do present earlier, due to nonspecific symptoms,[3,4]as is the case in our patient. Early diagnosis and treatment may improve survival. But this is often a challenge in developing countries due to lack of required diagnostic facilities for optimum patient's evaluation and difficulty accessing effective medications. Without treatment, the prognosis is worse in children compared to adults.[3] There is paucity of documented data on idiopathic PH among paediatric patients in Nigeria. Hence, we report the occurrence of such case seen in our centre.

II. Case Report

H.R, a 3-year-old girl presented with recurrent breathlessness, cough and body swelling since the age of 3 months. She had history of feeding difficulty that started around 5 months of age but no cyanosis. She was referred for further evaluation on account of persistent symptoms despite treatment for pneumonia and 2 months course of anti-tuberculous drugs.

On general physical examination, she was small for age, weight was 7.8 Kg (less than 3rd centile) and height was 79 cm (less than 5th centile). She was in obvious respiratory distress, dusky with grade II digital clubbing; neck veins were prominent with mild puffiness and bilateral pitting pedal and leg oedema. Pulse oxygen saturation was 97% in room air and no facial dysmorphism.

Cardiovascular examination revealed normal volume pulses, regular with pulse rate of 164 beats per minute. Blood pressure was 90/50 mmHg. Jugular venous pressure (JVP) was raised. There was mild precordial bulging with left parasternal heave and palpable second heart sound. Apical impulse was at 5th left intercostal

space anterior axillary line. First heart sound was normal with loud single pulmonary component of the second sound and a grade II pansystolic murmur at the lower left sternal border. There was tender hepatomegaly with liver span of 13 cm; ascites was demonstrable by shifting dullness. Screening for tuberculosis, HIV and viral hepatitis were negative. Liver and renal functions were normal.

Electrocardiogram revealed sinus tachycardia, tall peaked P wave in lead II, prominent R wave in V1, upright T waves in V1-V3 and right axis deviation in keeping with right atrial and right ventricular hypertrophy. Chest X-Ray shows peripheral pruning with mild cardiomegaly (CT ratio of 0.58). Echocardiogram revealed dilated right atrium and ventricle with severe tricuspid regurgitation and supra-systemic pulmonary artery pressure, with normal pulmonary venous return. Pulmonary artery systolic pressure was 127 mmHg (mean pulmonary artery pressure of 42 mmHg) against systolic blood pressure of 90 mmHg.

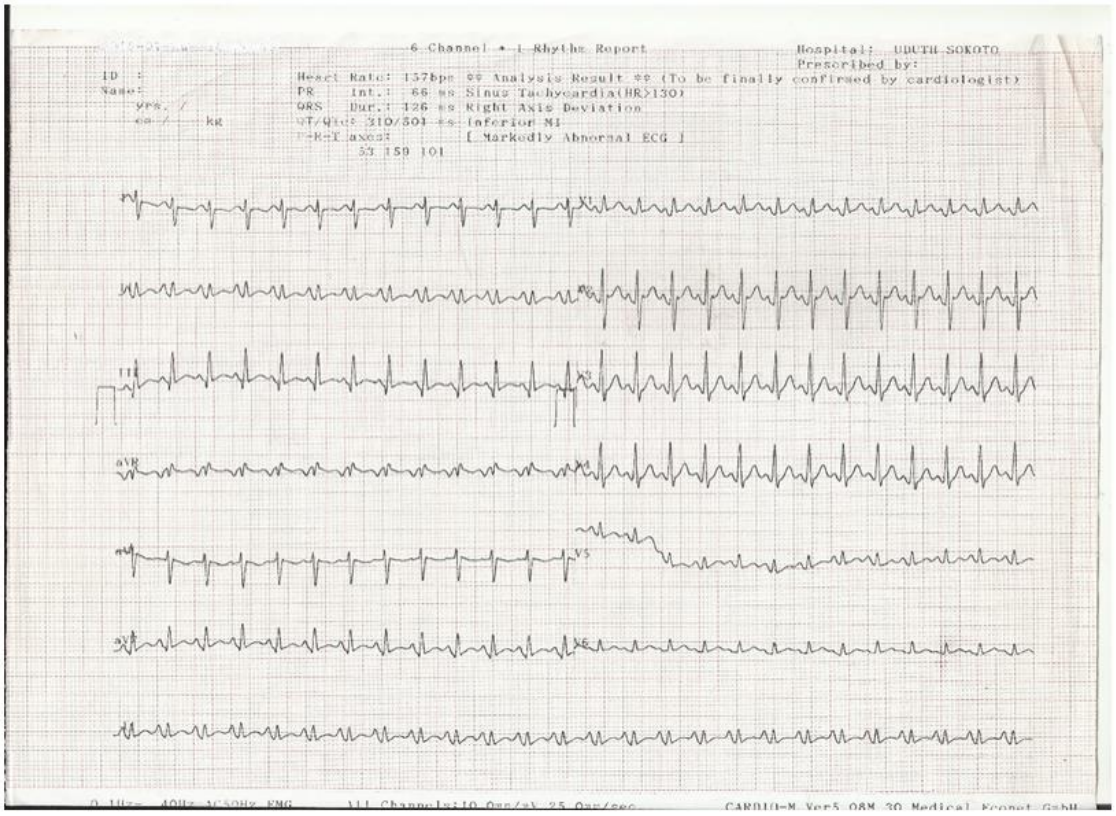

Figure 1: ECG of the patient showing normal sinus rhythm, tall peaked p waves in lead II indicative of right atrial enlargement, right axis deviation and prominent R waves in V1 with upright T waves in V1, V2 and V3 indicative of strain pattern right ventricular hypertrophy.

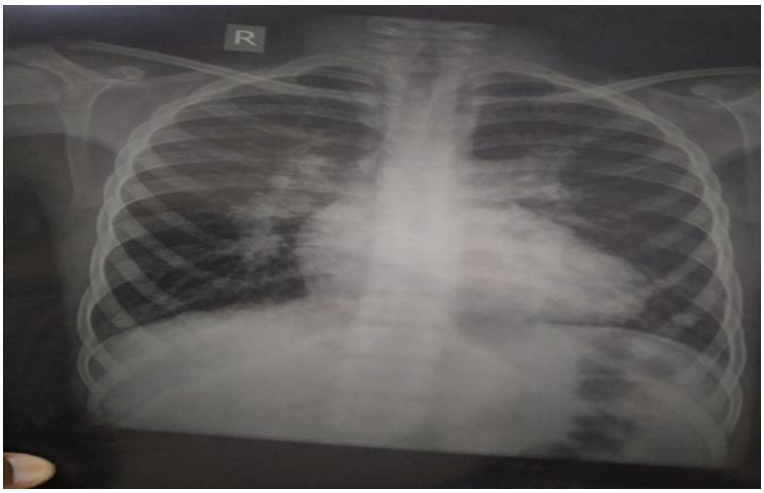

Figure 2: Chest X-Ray of the Patient showing peripheral pruning with mild cardiomegaly, cardiomegaly (CT ratio: 0.58) and upturned apex indicative of right ventricular hypertrophy

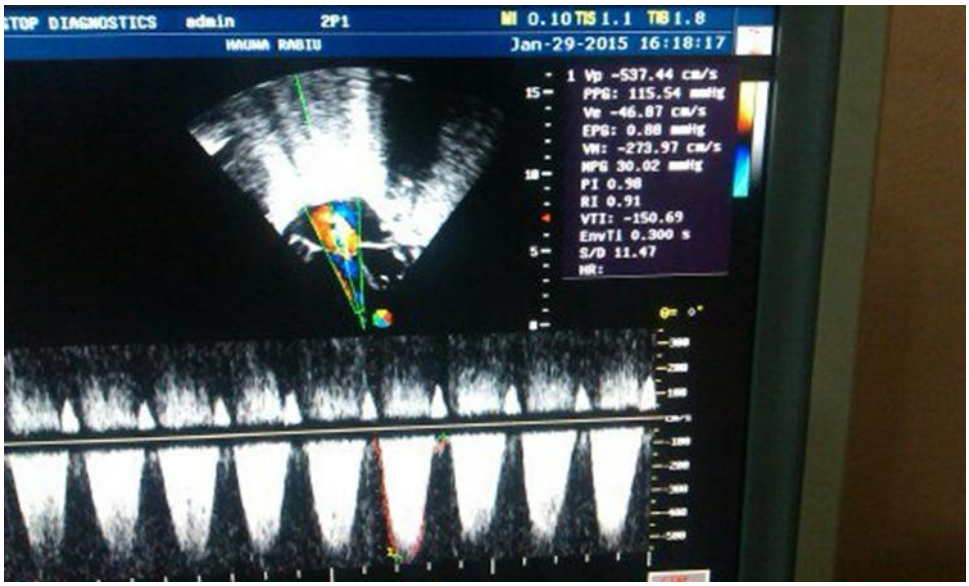

Figure 3: Colour flow and Continues wave Doppler from patient H.R. Note the tricuspid regurgitation jet and the time velocity integral. The peak tricuspid regurgitation velocity (TRV) was **5.37 m/s.** Right atrial pressure (RPA) of 12 mmHg (10% of $4V^2$).[5] Pulmonary artery systolic pressure of **127 mmHg** ($4V^2$ + RPA).[5] The mean pulmonary gradient (MG) was **30 mmHg** and mean pulmonary artery pressure (MPAP) was **42 mmHg (MG + RPA).[6]**

There was no identifiable structural heart disease to explain the elevation in pulmonary artery pressure. Facilities for cardiac catheterization, Cardiac CT and MRI were not available for further evaluation of the patient.

Patient was commenced on oral sildenafil initially at 0.5 mg/kg/dose three times daily and later increased to 1mg/kg with no significant improvement. Three weeks later; Bosentan was added orally at a dose of 1mg/kg twice a day. Repeat peak TRV after 3 weeks of dual therapy was 2.8 m/s with PASP of 34 mmHg and MPAP of 18 mmHg. She responded well to treatment as evidenced by resolution of clinical symptoms and reduction in pulmonary artery pressure. Patient was discharged home after 26 days of admission. Patient remained stable on sildenafil and Bosentan and was being followed up. Her clinical symptoms subsided, and serial liver function test were all normal.

Nine months after discharge, Bosentan got finished and parents were unable to continue sourcing for Bosentan outside the country as the drug was not available in the country at the time; she was continued on sildenafil alone. Two months after discontinuing Bosentan, symptoms reoccurred with worsening dyspnoea, abdominal swelling and legs swelling. After about 3 months parents defaulted follow up for 6 weeks and later were re-admitted with severe respiratory failure. She subsequently succumbed to the illness 18 months after the diagnosis.

III. Discussion

Pulmonary hypertension is associated with diverse cardiac, pulmonary, and systemic diseases in neonates, infants, and older children that can present at any age, and cause significant morbidity and mortality.[5] Idiopathic pulmonary artery hypertension (IPAH) is a pulmonary vasculopathy that remains a diagnosis of exclusion, specifically indicating the absence of diseases of the left side of the heart or valves, lung parenchyma, thromboembolism, or other miscellaneous causes.[6] In our patient, echocardiography reveals no significant structural heart disease that can explain the level of elevation in pulmonary pressure. There were no significant lung lesions on chest X ray, and other investigations done including complete blood count, Erythrocyte sedimentation rate, tuberculin skin test, gastric washout for Acid Fast Bacilli and Gene Xpert were all negative.

PH is known to present at any age from the neonatal period to adulthood.[5,6] Paucity of data on the disease in developing countries as well as draught in interest by few paediatric cardiologist and pulmonologist around, have limited the care of paediatric patients with pulmonary hypertension. This is further compounded by lack of consensus guidelines from experts in the field. Although there is still no cure for PAH, quality of life and survival have been improved significantly with specific drug therapies.[7]

Regardless of the aetiology, clinical manifestations of pulmonary hypertension are similar.[1,2] Though not limited to the heart, but most of the burden of the disease is bears by the heart. Symptoms are mostly related to the degree of pulmonary arterial pressure elevation and the status of the right ventricle.[8,9] The predominant

symptoms in this patient were those of congestive cardiac failure with failure to thrive. These symptoms are often difficult to differentiate from those caused by other pulmonary or cardiac disorders.

Central pulmonary artery enlargement with peripheral pruning of pulmonary vasculature and right ventricular enlargement are seen on chest X-ray of patients with PH. As pulmonary blood flow decreases, the lung fields become oligaemic. Calcification of the central pulmonary arteries has been associated with thrombosis.[1,2] Chest X-ray in this patient show pruning of central pulmonary vessels with peripheral oligaemia. ECG shows right atrial enlargement, right ventricular hypertrophy (RVH), right axis deviation and secondary T-wave changes typical of PH.[1,2] Right heart catheterization (RHC) using high-fidelity pulmonary artery catheters is the gold standard in establishing the diagnosis of PH.[10]

In our centre, facility for RHC were not available and pulmonary hypertension was diagnosed in our patient non-invasively using echocardiography by estimating MPAP using the mean gradient method (MG),[11,12] developed on the basis of a modification of the traditional echocardiographic method of calculating SPAP. The method involves addition of right atrial pressure to the right ventricular-right atrial mean systolic gradient instead of peak systolic gradient. The right atrial pressure was estimated as 10% of $4V^2$,[13] where V is the peak tricuspid regurgitant velocity. This method was evaluated both retrospectively by Bishop *et al*,[14] and prospectively,[15] and shows satisfactory limits of agreement and correlation between echocardiographically determined MPAP and RHC measured MPAP. The MPAP in this patient was 42 mmHg as depicted in figure 1 above.

IPAH in paediatric patients can be devastating and often contributes to poor outcomes. Unfortunately, there are only few studies that specifically address the safety and efficacy of drug therapies in children. Paediatric PH has been understudied, and little is understood about the natural history, fundamental mechanisms, and treatment of childhood PH. In recent time, with the advent of high tech paediatric cardiac care, coupled with the fact that PH can complicate variety of childhood illnesses, more children with pulmonary hypertension are being encountered in day-to-day paediatric practice. Therefore, there is urgent need to better define the natural history and course of paediatric PH, to develop new strategies to identify patients at risk for the development of PH, and to establish novel approaches to diagnose, to monitor the disease progression of, and to treat children with PAH.

Without treatment, estimated median survival after diagnosis of patients with IPAH is reported to be dismal, i.e., 0.8 year in children and 2.8 years in adults.[16] The therapeutic goal is the remodelling of the pulmonary vasculature back to normal, the restoration of endothelial function and the growth of new peripheral pulmonary arteries.[17] Most children require dual therapy as sildenafil has not been proven to be efficacious in children.[17] In this patient, she was initially commenced on sildenafil alone, as most other agents are not readily available in the country. Due to poor response, bosentan was ordered from Abroad with the assistance of the caring physicians and patient was continued on dual agents with significant improvement both clinically and echocardiographically.

She was followed up after discharge as urgent intensification of therapy is frequently necessary. The UK Pulmonary Hypertension Service showed survival figures of 84% at 1 year and 76% at 3 years.[18] This patient survived for 18 months on treatment after diagnosis. New endothelin receptor antagonists and new PDE 1/5/6 plus PDE-3 and PDE-1 inhibitors are in development now. Statins, RhoA inhibitors, anti-growth factor drugs, metalloproteinase inhibitors, K channel openers, stem cell and gene therapy and vasoactive intestinal peptide are all under investigation. These newer modalities in combination may offer the hope of cure and greater promise of tailoring the treatment to the individual child. Patients who fail to respond to medical therapy are offered the possibility of lung transplantation. The predicted survival for lung transplantation in children is 4.3 years with a 75% survival at 1 year,[19] when presented late but early diagnosis and prompt institution of management improves outcome significantly.[20]

IV. Conclusion

Idiopathic PH presents with non-specific symptoms in children leading to delay in the diagnosis of this condition. Although the gold standard for establishing the diagnosis is right heart catheterization, it is not readily available in this part of the world. Newer echocardiographic methods of estimating MPAP from the area under the curve of the tricuspid regurgitation jet, can help significantly in ameliorating the diagnostic challenges in the absence of right heart catheterization facility; institution of drug treatment and improvement of outcome. Therapeutic agent for pulmonary hypertension therapy and facilities for right heart catheterization should be made readily available to allow for a more accurate diagnosis and treatment.

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