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A Rare Cause for Unsuccessful Catheter Intervention for Congenital Pulmonary Valve Stenosis: MYHRE Syndrome

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Abstract: ***MYHRE syndrome (MS) is a rare connective tissue disorder characterized by various systemic abnormalities. Cardiovascular anomalies like aortopathies, restrictive cardiomyopathy, persistent arterial duct and Shones complex had been mentioned previously but the outcomes with or without interventions have been poor. Here, we present a case of Myhre syndrome and congenital pulmonary valve stenosis refractory to catheter valvotomies and requiring surgical intervention.***

Keywords: Myhre Syndrome, Connective tissue disorder, Catheter intervention

1. Introduction

MYHRE syndrome is a rare connective tissue disorder characterized by short stature, neurodevelopmental delay and various systemic abnormalities[1]. First diagnosed in 1981, there have been approximately 100 patients reported in the literature with 80 patients having molecular confirmation[2]. Associated cardiovascular anomalies include aortopathies, restrictive cardiomyopathy, pericardial disease and other congenital heart defects, but the outcomes had been dismal[3]. Failed interventions like balloon aortic valvotomies have been reported in these patients[3]. Here, we present our experience with a case of Myhre syndrome with congenital pulmonary valve stenosis refractory to catheter valvotomies, requiring surgical intervention. This is the first case to be reported from India.

2. Case Summary

7-year-old patient, first born out of non-consanguineous marriage, was delivered at 32 weeks of gestation with birth weight of 1.7 kg. Patient was diagnosed with congenital pulmonary valvar stenosis at birth and was in close follow up. At the age of 3 months, patient underwent first balloon valvotomy and post procedural echo showed satisfactory result. The peak gradient across the pulmonary valve dropped from 70mm Hg to 37mmHg. Patient was lost for follow up for almost 4-years due to financial constraints. At the current visit, patient was brought in by the parents with complain of dyspnea on exertion with easy fatiguability.

2D echocardiogram showed severe pulmonary valve re-stenosis (Peak gradient - 77 mm Hg) with mild supravalvar tethering. In addition, there was left pulmonary artery origin stenosis and a tiny patent ductus arteriosus. Second balloon pulmonary valvotomy **(Figure 1 & 2)** was thus performed and pre discharge, patient had a gradient of 40 mm Hg across the pulmonary valve with no flow acceleration in the left pulmonary artery. However, follow up echocardiography at 3 months showed severe pulmonary valve obstruction with left pulmonary artery origin stenosis and tiny Patent ductus arteriosus. Patient was then referred for surgical intervention.

Meanwhile, the patient underwent genetic analysis. Whole exome sequencing was performed for the patient and the study turned out to be positive for gene mutation of SMAD4. Along with the clinical features, the mutation helped in diagnosing of Myhre syndrome.

Case was discussed in the multidisciplinary meeting and decided on surgical intervention owing to the patient symptoms. However, chances of recurrence were thoroughly discussed and conveyed to the parents as well.

Intraoperatively, pulmonary valve annulus was small, pulmonary valve was tricuspid, dysplastic with narrow orifice area. In addition, there was left pulmonary artery origin narrowing. A biopsy sample was taken from right ventricular endocardium. A trans-annular patch with left pulmonary arterioplasty was performed using tanned autologous pericardial patch.

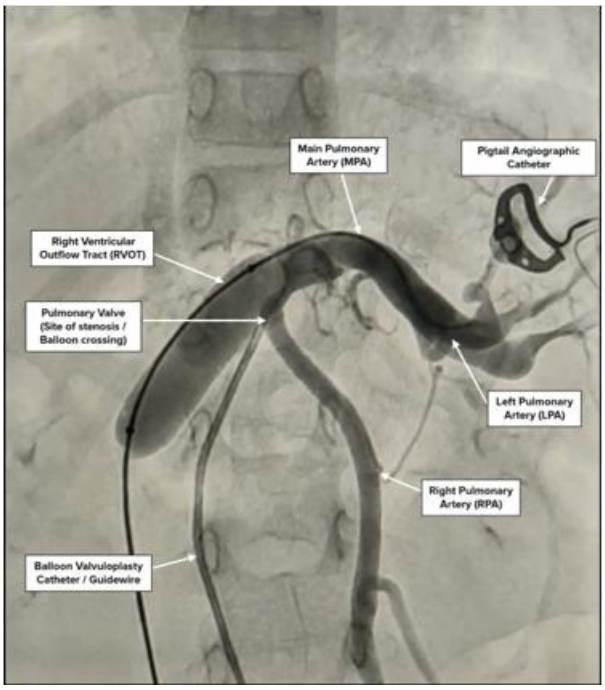

Figure 1: Pre-intervention right ventricular angiogram before balloon pulmonary valvotomy

Figure 1: Right ventricular outflow tract (RVOT) angiogram in a 7-year-old girl with genetically confirmed Myhre syndrome demonstrating severe congenital valvular pulmonary stenosis. Contrast injection outlines the hypertrophied RVOT, narrowed pulmonary valve annulus, and post-stenotic dilatation of the main pulmonary artery (MPA). The right (RPA) and left pulmonary arteries (LPA) are visualized. A balloon valvuloplasty catheter is positioned across the stenotic pulmonary valve while a pigtail catheter is used for angiographic assessment. This image illustrates the anatomy immediately before balloon pulmonary valvotomy.

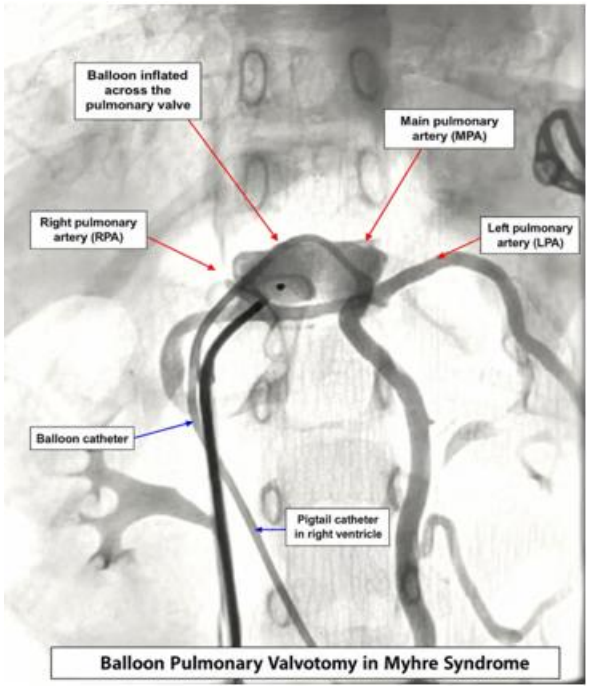

Figure 2: Balloon pulmonary valvotomy in Myhre Syndrome

Figure 2: Fluoroscopic image obtained during balloon pulmonary valvotomy showing complete inflation of the balloon across the stenotic pulmonary valve. The characteristic waist of the balloon at the level of the valve represents the site of maximal obstruction and confirms severe valvular stenosis. Simultaneous angiography delineates the main pulmonary artery and its bifurcation into the right and left pulmonary arteries. The image demonstrates the interventional treatment performed for recurrent pulmonary valve obstruction in a child with Myhre syndrome, a disorder characterized by progressive fibroproliferative tissue response and a high propensity for restenosis

Perioperative period was uneventful and the patient was discharged home on 5th postoperative day. Discharge 2D echocardiogram showed good ventricular function and free pulmonary regurgitation, good flow in the branch pulmonary arteries. At 3 month follow up, the patient was asymptomatic. 2D echocardiogram at 3 months demonstrated free pulmonary regurgitation with good flow in the branch pulmonary arteries, a gradient of 17 mm Hg in the left pulmonary artery and moderate pericardial effusion. The patient underwent uneventful pericardial fluid drainage.

Endomyocardial biopsy showed thickened, fibrosed and hyalinized endocardium. The myocardium showed thickening, disarray and hypertrophy with muscle nuclei showing mild degree of pleomorphism **(Figure 3)**. These features are compatible with Myhre syndrome

3. Discussion

Myhre syndrome is a rare genetic disorder with only 100 diagnosed cases in the literature and only about 80 patients with molecular confirmation[2]. Thus, ours will be an addition to this short list with confirmed gene mutation. There are certain features which are consistently present in each case like short stature, facial dysmorphism, joint limitation[4]. There are very few case reports mentioning failed interventions due to inherent risk of extensive fibroproliferative response to any sort of intervention or trauma[5].

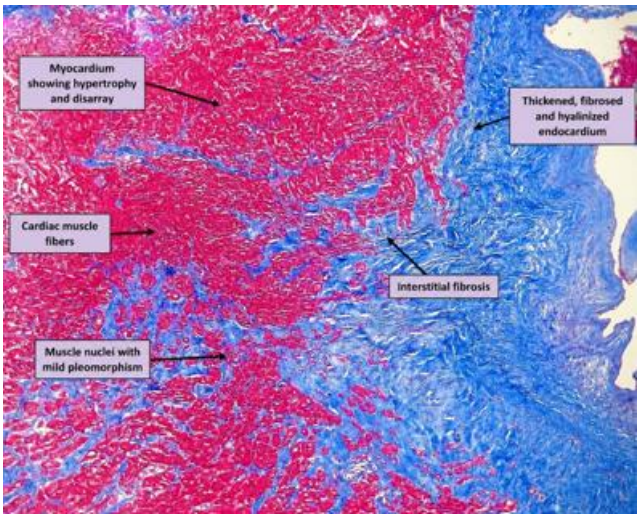

Figure 3: Histopathological description: Masson's trichrome–stained section of a right ventricular endomyocardial biopsy from a 7-year-old patient with genetically confirmed Myhre syndrome demonstrates

marked endocardial thickening with dense collagenous fibrosis, staining blue. Fibrosis extends into the underlying myocardium, producing prominent interstitial and replacement fibrosis between the red-staining cardiac muscle fibres. The myocardium shows cardiomyocyte hypertrophy and architectural disarray. These findings indicate significant endomyocardial fibrotic remodelling and are consistent with the cardiac involvement described in Myhre syndrome associated with a pathogenic SMAD4 variant.

In this case, patient had triangular facies, with small earlobes, short philtrum, short stature, clinodactyly of 5th finger and bilateral undescended testes. Patient`s clinical examination along with the whole exome sequencing test correlated with the diagnosis of this syndrome. Our patient has a proven **SMAD4 mutation with 1498A>G nucleotide change**[6]. The report stated an Ile500 at ile500Val transition which is found to be more common compared to other transitions. The incidence of cardiovascular anomalies is as high as 70% with majority being congenital heart defects (63%). Among congenital heart defects, left sided lesions like Shones are more common. Amongst the rare cases with right sided structural involvement, there is one case reported with pulmonary valve stenosis and 2 cases with branch pulmonary artery stenosis in the literature[7,8]. Our case presented with pulmonary valve stenosis and progressively developing left pulmonary artery stenosis.

We here aim to report our experience with the first proven case with cardiac anomaly from India and shed some light on the management of Myhre syndrome with cardiovascular anomaly needing multiple interventions. SMAD4 gene is involved in signal transduction pathway for TGF-β. A gain of function mutation results in exaggerated cellular response with increased sensitivity to fibrotic and calcific cellular signaling and the findings consistent with cardiac and pulmonary fibrosis. Such patients have abnormal healing process which may impact overall success of intervention, morbidity and mortality of these patients.

These pathological findings may explain the cause of failed intervention and disease progression in these patients[2]. As previously mentioned by Starr et al, balloon angioplasty has been performed for aortic valve stenosis and proved to be refractory and the patient had to undergo surgical intervention. These patients even after intervention require prolonged follow up and may require heart transplant due to extensive fibrosis and development of Restrictive cardiomyopathy and heart failure[3]. In our case, pulmonary valvar stenosis proved to be refractory to intervention and finally patient had to undergo an open cardiac procedure Parents were counselled for the need for prolonged follow up, the resistant and recurring nature of the pathology and need for further interventions if required.

Thus, intervention in patients with Myhre syndrome needs to be discussed because of the abnormal healing process and the impact on survival of the patient. If required, there should be minimal tissue handling and tissue trauma. Post-operatively the patient must be monitored for abnormal wound healing. Follow up with serial echocardiograms for the detection of progressive valvar and myocardial disease is mandatory.

To conclude, patients with Myhre syndrome have a high chance of having a cardiovascular anomaly which may be refractory to any form of intervention. Any intervention may lead to clinical deterioration of the patient if not performed with utmost care. Post-intervention surveillance is mandatory to detect the disease progression and to implement appropriate management strategy.

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Conflicts of interest: None

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Figure legends:
Figure 1. Pre-intervention right ventricular angiogram before balloon pulmonary valvotomy
Figure 2. Catheterization and balloon pulmonary valvotomy
Figure 3: Histopathological picture showing endomyocardial hypertrophy with fibrosis (Masson`s Trichrome Stain.10x)