Rev Med Int Sindr Down. 2014;**18(1)**:9-12

INTERNATIONAL MEDICAL REVIEW ON DOWN'S SYNDROME

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FUNDACIÓ CATALANA SÍNDROME DE DOWN
www.fcsd.org

CASE REPORT

The role of cardiac catheterization in Trisomy 21 and pulmonary hypertension

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Received on January 10, 2014; accepted on February 24, 2014

KEY WORDS
Pulmonary hypertension;
Pulmonary arterial hypertension;
Trisomy 21;
Cardiac catheterization

Abstract
Children with Trisomy 21 are at increased risk for pulmonary hypertension. The reasons for this are multi-factorial but include an abnormal pulmonary vascular bed with increased propensity for congenital heart disease and upper airway obstruction. And although the association of pulmonary hypertension with Trisomy 21 is well established, this case report highlights the complexity of pulmonary hypertension in this vulnerable population, the limitations of echocardiography and critical contribution of cardiac catheterization in informing clinical management.

PALABRAS CLAVE
Hipertensión pulmonar;
Hipertensión arterial pulmonar;
Trisomía 21;
Cateterismo cardíaco

El papel del cateterismo cardíaco en la trisomía 21 y en la hipertensión pulmonar

Resumen
Los niños con trisomía 21 presentan un mayor riesgo de sufrir hipertensión pulmonar. Los motivos son multifactoriales, pero incluyen un lecho vascular pulmonar anómalo con mayor propensión a cardiopatía congénita y obstrucción de las vías respiratorias superiores. Y a pesar de que la asociación de la hipertensión pulmonar con la trisomía 21 está bien fundamentada, este caso clínico señala la complejidad de la hipertensión pulmonar en esta población vulnerable, las limitaciones de la ecocardiografía y la contribución crucial del cateterismo cardíaco aportando información para la gestión clínica.

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Introduction

Trisomy 21 is one of the most commonly cited genetic disorders to occur in association with pulmonary hypertension and is the most commonly occurring trisomy in humans with an incidence of 16 per 10,000 births[1,2]. Children with Trisomy 21 are at risk for multiple cardiopulmonary issues including upper airway obstruction, lower airway anomalies, and congenital heart disease. In addition, children with Trisomy 21 may have intrinsic abnormalities of the pulmonary vascular bed that increases their risk for pulmonary arterial hypertension (PAH) with and without congenital heart disease in comparison to individuals without Trisomy 21[3,4]. Pulmonary hypertension is a general term used to indicate elevated pressure in the pulmonary artery circuit which can result from increased pulmonary vascular resistance (PAH) or impaired pulmonary venous drainage (PVH) either from anatomical obstruction or left ventricular diastolic dysfunction. PAH is defined as an elevation in mean pulmonary artery pressure (mPAP) of > 25 mmHg in the presence of a normal pulmonary capillary wedge pressure and pulmonary vascular resistance index (PVRI) > 3 Wood Units (WU/m^2), resulting in impaired blood flow to the lungs and clinical signs of heart failure[5]. These hemodynamic findings distinguish PAH from PVH which may not be amendable to pulmonary vasodilator therapy. And although PAH may resolve with time and close clinical observation in most patients with Trisomy 21, persistent signs of heart failure related to PAH requires a detailed evaluation.

Clinical Observation

Patient 1

Patient one was a full term female infant born after an uneventful pregnancy with Trisomy 21. APGAR scores were 8 and 9 at one and five minutes, respectively. The patient experienced hypoxemia soon after birth which was corrected with supplemental oxygen at a flow of 1 lpm. Echocardiogram performed on day of life (DOL) 6 revealed a moderate sized patent ductus arteriosus (PDA) with left to right flow, although flow velocity was noted to be decreased indicating elevated pulmonary artery (PA) pressures. Then an echocardiogram performed on DOL 11 revealed a 4 mm secundum atrial septal defect (ASD) with left to right flow, mild right ventricular (RV) dilatation with decreased RV contractility, and small PDA; right ventricular systolic pressure (RVSP) was estimated at 40 mmHg. Because the infant had persistent hypoxemia, she was discharged home on supplemental oxygen. During the ensuing two weeks, the infant was noted to have diaphoresis during feedings, excessive sleepiness but no cyanosis. These symptoms failed to improve in response to the initiation of ranitidine and transition to caloric dense formula. Serum concentration of brain naturetic peptide (BNP), TSH, T4 and T3 were normal. Echocardiogram performed at ~ 3 months of age revealed moderate dilation of the right ventricle and right atrium, dilation of the pulmonary artery, and a small PDA. The RVSP was estimated at 45–50 mmHg and the flow velocity across the PDA was slow, predicting near systemic PA pressures. A cardiac catheterization was performed. On room air, the mPAP was elevated at 28 mmHg, whereas the value of the pulmonary capillary wedge pressure (PCWP) and pulmonary vascular resistance index (PVRI) were within normal range at 8 mmHg and PVR 1.86 WU/m^2. The pulmonary blood flow:systemic blood flow (Qp:Qs) was elevated at 2.67; this was accounted for by a large PDA that was identified by angiography and successfully closed with an Amplatzer device (fig. 1A and B). Post PDA closure, the values of mPAP, PVRI, and Qp:Qs were 21 mmHg, 2.19, and 1.56, respectively. The infant experienced resolution of symptoms with improved growth rate and activity.

Patient 2

Patient two was born a full term, female infant after an uneventful pregnancy. The infant's APGAR scores were 8 and 8 at one and five minutes, respectively. The infant had Trisomy 21 and duodenal atresia which was surgically repaired on DOL 2. Post-operatively, the infant received non-invasive positive pressure ventilation and supplemental oxygen but this was weaned off prior to discharge home at 3 weeks of age. Echocardiograms performed on DOL 1 revealed the following: a fenestrated ASD, right atrial enlargement (RAE), mild RVH and large PDA with low velocity left to right flow. Echocardiograms performed on DOL 10 and 21 confirmed the findings of the initial echocardiogram revealing a secundum ASD, RAE, RVH and small PDA. The peak tricuspid regurgitant jet velocity (TRJV) was 4 m/s, which predicts a RVSP of 64 mmHg. The infant was admitted to the hospital at four months of age with labored breathing: serum BNP concentration was elevated at 284 pg/ml. The infant's clinical status failed to improve in response to therapy with furosemide and supplemental oxygen; thus, she underwent surgical ligation of the ductus arteriosus, a procedure which was complicated by chylothorax. This then required thoracic duct ligation and pleurodesis. After fifteen days the patient was discharged home on furosemide, spironolactone, supplemental oxygen at 0.25 L/min and omeprazole. An echocardiogram performed prior to discharge revealed a large ASD with left to right shunt, anomalous drainage of the right upper pulmonary vein to the RA, moderate to severe RV dilatation with flattening of the intra-ventricular septum, and elevation of the RVSP at 55–66 mmHg. Two weeks after discharge the patient was readmitted to the Pediatric Intensive Care Unit (PICU) with increased work of breathing and hypoxemia. Therapy with supplemental oxygen, furosemide, and bronchodilators was associated with a clinical improvement reflected by a decrease in serum BNP from 721 pg/ml on admission to 179 pg/ml by hospital day 2. The evaluation of the patient was completed with cardiac catheterization. On room air the value for mPAP was elevated at 35 mmHg, whereas the value for PCWP was in the normal range at 6 mmHg. The PVRI and Qp:Qs were estimated at 3.84 WU/m^2 and 1.63, respectively. The application of 100% oxygen plus iNO at 40 ppm was associated with a decrease in mPAP and PVRI to 27 mmHg and 2.26 WU/m^2, respectively and increase in Qp:Qs to 2.42. Angiography revealed normal arborization of the pulmonary artery (fig. 1C), but demonstrated anomalous

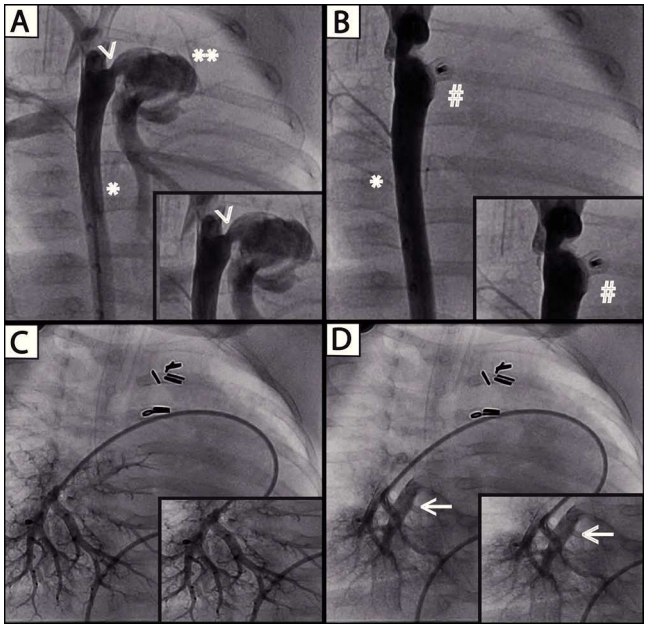

Figure 1 Pulmonary Angiography. A) Left to right shunting is seen through a large patent ductus arteriosus (PDA) with clear identification of main pulmonary artery and PA branching. B) Successful closure of PDA with no visible shunting from aorta to pulmonary artery. C) Demonstrates normal 'blush' with manual injection of contrast into the right pulmonary artery. D) Anomalous drainage of right pulmonary vein to right atrium. *Aorta, **pulmonary artery, >patent ductus arteriosus, #Amplatzer device occluder, →anomalous right lower pulmonary vein.

drainage of the right upper pulmonary vein to the superior vena cava-right atrial junction and right lower pulmonary vein drainage into the right atrium (fig. 1D). The patient underwent definitive cardiac repair of her partial anomalous pulmonary venous return (PAPVR). In the following weeks the patient tolerated weaning of supplemental oxygen, as well as, diuretic therapy. Feeding tolerance improved as did acquisition of motor milestones.

Discussion

In the current case report both patients presented with pulmonary hypertension in association with Trisomy 21. Despite their similar presentation, including clinical signs of heart failure and similar echocardiogram findings, the etiology of each patient's pulmonary hypertension was distinct indicating the complexity of pulmonary hypertension in this population. Echocardiography continues to serve as the primary screening method for pulmonary hypertension as it did in the above cases; however echocardiography has noted limitations. These include decreased accuracy at higher RVSPs in comparison to cardiac catheterization, as well as, under appreciation of cardiac shunts and inability to identify critical cardiac lesions such as pulmonary vein stenosis which can mimic PAH and has been associated with Trisomy 21[6-8]. In addition, because pressure is a function of both resistance and flow (derived from Ohm's law: Pressure = Resistance x Flow), increased RVSP identified with echocardiography can stem from increased pulmonary blood flow, increased pulmonary vascular resistance or a combination of the two. Thus, understanding the hemodynamic etiology of pulmonary hypertension is critical, but limited based on echocardiography data alone.

Cardiac catheterization is relatively safe in pediatric patients with pulmonary hypertension when performed by experienced practitioners and is required in patients with suspected PAH to confirm hemodynamic findings, including vasodilator testing and exclude anatomical cardiac defects that can contribute to the development of pulmonary hypertension[9]. In both cases hemodynamic data acquired during cardiac catheterization revealed increased pulmonary blood flow resulting in PAH. In addition, patient one underwent Amplatzer device closure of her PDA which resulted in resolution of PAH negating the need for an additional procedure. This case report also highlights the risks of empiric initiation of pulmonary vasodilator therapy in PH based only on echocardiography data. Although pulmonary vasodilator therapy initiated for PAH characterized by increased pulmonary vascular resistance has resulted in improved survival in pediatric patients, in the current cases this would have likely not been effective and perhaps led to clinical deterioration[10].

In conclusion patients with Trisomy 21 are at increased risk for the development of PAH with or without associated congenital heart disease. Echocardiography serves as a useful tool for screening and prospective observation; however, is associated with specific limitations with regard to precise quantification of severity of pulmonary hypertension, congenital shunts and identification of cardiac anomalies. This case report strongly indicates that children with Trisomy 21 with signs of persistent pulmonary hypertension especially when associated with heart failure may benefit from cardiac catheterization to better inform clinical decision making and improve outcomes.

References

1. Berger RM, Beghetti M, Humpl T, Raskob GE, Ivy DD, Jing ZC, et al. Clinical features of paediatric pulmonary hypertension: a registry study. Lancet. 2012;379:537-46.
2. Weijerman ME, van Furth AM, Vonk NA, van Wouwe JP, Broers CJ, Gemke RJ. Prevalence, neonatal characteristics, and first-year mortality of Down syndrome: a national study. J Pediatr. 2008;152:15-9.
3. Cooney TP, Thurlbeck WM. Pulmonary hypoplasia in Down's syndrome. N Engl J Med. 1982;307:1170-3.
4. Bertrand P, Navarro H, Caussade S, Holmgren N, Sanchez I. Airway anomalies in children with Down syndrome: endoscopic findings. Pediatr Pulmonol. 2003;36:137-41.
5. Cerro MJ, Abman S, Diaz G, Freudenthal AH, Freudenthal F, Harikrishnan S, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: Report from the PVRI Pediatric Taskforce, Panama 2011. Pulm Circ. 2011;1:286-98.
6. Holcomb RG, Tyson RW, Ivy DD, Abman SH, Kinsella JP. Congenital pulmonary venous stenosis presenting as persistent pulmonary hypertension of the newborn. Pediatr Pulmonol. 1999;28:301-6.
7. Groh GK, Levy PT, Holland MR, Murphy JJ, Sekarski TJ, Myers CL, et al. Doppler echocardiography inaccurately estimates

right ventricular pressure in children with elevated right heart pressure. J Am Soc Echocardiogr. 2014 feb;27(2):163-71.
8. Gowda S, Bhat D, Feng Z, Chang CH, Ross RD. Pulmonary vein stenosis with Down syndrome: A rare and frequently fatal cause of pulmonary hypertension in infants and children. Congenit Heart Dis. 2013. May 8 [Epub ahead of print].
9. Hill KD, Lim DS, Everett AD, Ivy DD, Moore JD. Assessment of pulmonary hypertension in the pediatric catheterization laboratory: current insights from the Magic registry. Catheter Cardiovasc Interv. 2010;76:865-73.
10. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart. 2010;96:1401-6.