Clinical Case Report

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Familial clustering of congenital deafness, patent ductus arteriosus, Eisenmenger complex, and differential cyanosis

A case report

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Abstract

Rationale: Few studies had reported syndromes that include patent ductus arteriosus (PDA) with Eisenmenger syndrome and congenital deafness clustered in male siblings without facial, skeletal, or mental abnormalities.

Patient concerns: Two brothers, who were deaf and had PDA with Eisenmenger complex, were first seen at our Cardiology clinic at the ages of 25 and 41, respectively. They presented with progressive dyspnea on exertion. Upon physical examination, both brothers had clubbing and/or cyanotic toes, normal fingers, and without facial, skeletal, ophthalmological, or mental abnormalities.

Diagnoses and interventions: Echocardiography and multidetector computed tomography revealed large PDAs in both brothers. Cardiac catheterization showed bidirectional shunting via the PDA.

Outcomes and lessons: Familial clustering of Eisenmenger PDA and congenital deafness is rare. Further studies are warranted to define possible genetic links.

Abbreviations: MDCT = multidetector computed tomography, PDA = patent ductus arteriosus.

Keywords: congenital deafness, differential cyanosis, Eisenmenger complex, patent ductus arteriosus

1. Introduction

Patent ductus arteriosus (PDA) is a form of congenital heart disease characterized by persistent patency between the descending aorta and the proximal pulmonary artery, which leads to a left-to-right shunt from the aorta to the pulmonary artery. The shunting could increase left atrial and left ventricular preload and induce pulmonary hypertension.[1,2] Patients with a large PDA and a significant shunt may present with clinical manifestations of congestive heart failure or, at a later stage, with reverse shunting and Eisenmenger syndrome.[2]

Although most cases of PDA are apparently sporadic, many are believed to be associated with multifactorial inheritance with a genetic predisposition or environmental triggers.[2] The chance of a PDA in a subsequent offspring if a sibling has a PDA is 3%.[2] Rubella infection during the first trimester of pregnancy is also associated with a high incidence of PDA.[3] However, few studies had reported any syndromes that include Eisenmenger syndrome, PDA, and congenital deafness clustered in male siblings without facial, skeletal, or mental abnormalities. A familial clustering of such abnormalities including congenital deafness, PDA, Eisenmenger complex, and differential cyanosis is outlined in this report.

2. Case presentation

The younger brother, who was 25-year-old at presentation, first visited our clinic in 2011 for a functional class II dyspnea on exertion lasting several months. Physical examination revealed a loud P2 but no continuous murmur over the left upper sternal border. His toes were cyanotic but fingers looked unusual, which was compatible with the sign of differential cyanosis (Fig. 1A). The electrocardiogram revealed pressure-overload type right ventricular hypertrophy and chest radiography showed a dilated aortic knob and main pulmonary arteries in a shunt-flow pattern with plethora. Multidetector computed tomography (MDCT) disclosed a large, nonrestrictive type PDA (Fig. 2A). The cardiac catheterization confirmed a large PDA with bidirectional shunting (Eisenmenger complex). Oxygen sampling during cardiac catheterization revealed an ascending aortic O_2 saturation of 96% and a descending aortic O_2 saturation of 93%, which could support the physical finding of a differential cyanosis between fingers and toes.

Four years later (in 2015), his elder brother, who was 41-year-old, was referred to our clinic due to progressive dyspnea on

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Both patients gave their written informed consent for publication of this report.

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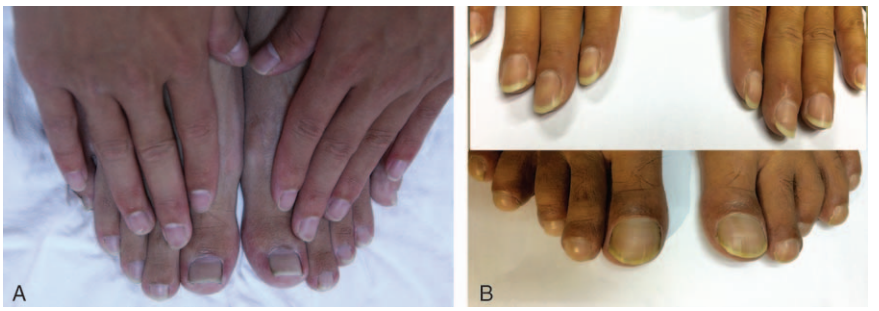

Figure 1. (A) The 25-year-old younger brother had differential cyanosis with cyanotic toes but normal fingers on physical examination. (B) The 41-year-old elder brother also had differential cyanosis with clubbing and cyanotic toes but normal fingers.

exertion. On physical examination, he had clubbing and cyanosis of his toes but normal-appearing fingers (Fig. 1B). In addition, his physical examination was notable for a loud P2 but no continuous murmur over the left upper sternal border found. Electrocardiogram revealed right atrial enlargement and right ventricular hypertrophy and chest radiography showed a dilated aortic knob and dilated main pulmonary arteries. The MDCT revealed a large (2.4 cm) PDA (Fig. 2B). The cardiac catheterization confirmed a large PDA with bidirectional shunting (Eisenmenger complex). The O_2 sampling was consistent with the presence of a right-to-left shunt with an ascending aortic O_2 saturation of 93% and a descending aortic O_2 saturation of 86%.

The 2 brothers had very similar clinical manifestations of congenital deafness and Eisenmenger PDA. They both grew up normally without mental retardation or facial or skeletal abnormalities. Their mother and a sister also had congenital deafness but no PDA. Another 3 sisters were healthy without deafness or PDA. Their father had passed away but did not have a history of deafness or PDA.

After diagnosis, the 2 brothers were put on endothelin receptor antagonist and phosphodiesterase type-5 inhibitor treatments for relief of the dyspnea due to the Eisenmenger PDA. Presently, they are both stable with functional class II symptoms.

The younger brother had a second hemodynamic measurement by cardiac catheterization 5 years after receiving endothelin receptor antagonist treatment. Compared with baseline data, the mean pulmonary arterial pressure had decreased from 89 to 71 mm Hg and mean systemic arterial pressure had decreased from 89 to 61 mm Hg after treatment. The O_2 sampling disclosed an ascending aortic O_2 saturation of 95% and a descending aortic O_2 saturation of 92%, indicating the persistent presence of a right-to-left shunt.

3. Discussion

To the best of our knowledge, this is the first case report to describe 2 brothers who presented in adulthood with congenital deafness and Eisenmenger PDA without facial, skeletal, or mental abnormalities.

PDA is correlated with rubella infection during pregnancy, premature birth, birth at a high altitude, family history, or other genetic conditions.[3–5] Both siblings in this case report were term infants by history, thus, preterm causes are excluded. Congenital rubella syndrome may comprise cardiac PDA, cerebral, ophthalmic, and auditory defects.[3] The maternal body would normally produce antibodies to the rubella virus once infected, thereby minimizing the possibility of repeated infection occurring in the next pregnancy. In our 2 cases, Eisenmenger PDA and congenital deafness happened twice in the offspring, thus maternal rubella infection is unlikely. PDA has been reported to occur in connection with other environmental factors such as fetal valproate syndrome.[6] However, both our cases denied any seizure or valproate exposure history.

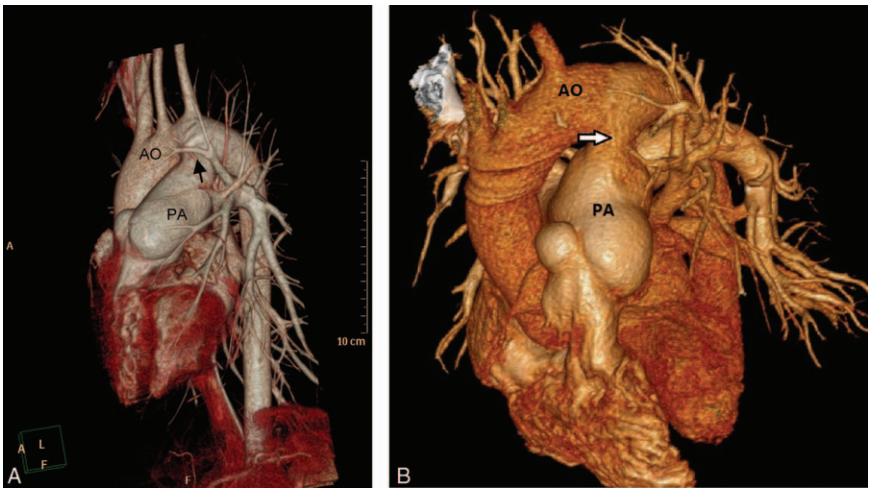

Figure 2. (A) MDCT of the younger brother revealed a large, nonrestrictive type PDA, 2.1 cm in diameter (arrow). (B) MDCT of the elder brother also showed a large (2.4 cm) PDA (arrow). AO = aorta, MDCT = multidetector computed tomography, PA = pulmonary artery, PDA = patent ductus arteriosus.

Several genetic syndromes have been reported to increase the incidence of PDA, including chromosomal aberrations, single-gene mutations, and X-linked mutations.[2] Common chromosomal aberrations, such as trisomy 21 (also known as Down syndrome) and 4p- syndrome (i.e., Wolf–Hirschhorn syndrome), have distinct craniofacial phenotypes.[7,8] Single-gene mutations include Carpenter's syndrome and Holt–Oram syndrome. The former is characterized by craniosynostosis, abnormalities of the fingers and toes, and other developmental problems.[9] Holt–-Oram syndrome features abnormalities of the upper limbs and heart.[10] Mutations in TFAP2B, which encodes a neural crest-derived transcription factor, can cause the abnormalities in Char syndrome, characterized by PDA, facial dysmorphism, and skeletal abnormalities of the hand.[11] CHARGE syndrome (Coloboma of the eye, Heart defects (including PDA), Atresia of the choanae, Retarded growth and development, Genital hypoplasia, and Ear anomalies and/or deafness) is a specific collection of nonrandomly occurring congenital anomalies caused by heterozygous mutation of CHD7 transmitted in an autosomal-dominant manner.[12] Myhre syndrome, a connective tissue disorder characterized by deafness, restricted joint movement, compact body habitus, and distinctive craniofacial and skeletal features, is caused by heterozygous mutations in SMAD4.[13] Cardiac manifestations in Myhre syndrome included PDA, septal defects, aortic coarctation, and pericarditis.[13] As both siblings in this report grew up normally (i.e., without mental, skeletal, or facial abnormalities), involvement of the aforementioned genetic syndromes is unlikely.

The hemodynamic change after endothelin receptor antagonist treatment in the younger brother was compatible with results from the BREATHE-5 study. That study showed that endothelin receptor antagonist treatment improved the functional status of Eisenmenger syndrome by decreasing both pulmonary arterial and systemic arterial pressure and resistance but had no impact on the shunting.[14]

For PDA with the presence of right-to-left shunting, current guidelines do not suggest simple closure of the shunt either by catheter or surgery.[15] Heart–lung or lung transplantation is an option in special cases not responsive to medical treatment, but is limited by organ availability.[15] Palliation with endothelin receptor antagonist or phosphodiesterase type-5 inhibitor may decrease pulmonary vascular resistance, decrease pulmonary arterial pressure, and improve functional status, as occurred in both of our cases.[14]

4. Conclusion

In this report, we presented rare clustering of congenital deafness, PDA with Eisenmenger complex, and differential cyanosis in male siblings within a family. Palliation with endothelin receptor antagonist may improve functional status as our cases did. Further studies are needed to define the possible genetic links.

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