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CASE REPORT

Berry Syndrome: A Possible Genetic Link

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Abstract Berry syndrome comprises a rare combination of heart defects that includes aortopulmonary window, interrupted aortic arch, intact ventricular septum, and aortic origin of the right pulmonary artery. We report the case of a neonate confirmed to have Berry syndrome by transthoracic echocardiogram and computed tomography (CT). This neonate had the additional finding of an aberrant right subclavian artery arising from the descending aorta. A single-stage repair was successfully performed when the infant was 7 days of age. Genetic testing showed a 102-kb deletion within chromosome band 9p24.2; this deletion has not been previously linked to congenital heart defects. Berry syndrome can be diagnosed accurately by transthoracic echocardiogram and CT. There may be an underlying genetic etiology, and this possibility warrants further investigation.

Keywords Aortopulmonary window · Interrupted aortic arch · Berry syndrome · Microarray testing

Introduction

Aortopulmonary window (APW) represents a rare form of congenital heart disease in which a connection exists between the ascending aorta and pulmonary artery above the semilunar valves. Although embryologically this involves the same region as other conotruncal defects, it is distinct from conotruncal lesions, such as persistent truncus arteriosus, and, unlike conotruncal lesions, is not thought to be the result of an abnormal development involving neural crest cells. Review of cardiac defects associated with DiGeorge syndrome has failed to demonstrate cases of APW associated with DiGeorge syndrome [4]. Interrupted aortic arch (IAA) represents discontinuity between the ascending and descending aorta. Berry syndrome comprises a rare combination of heart defects, including IAA, APW, intact ventricular septum, and aortic origin of the right pulmonary artery. We report the case of a neonate confirmed to have Berry syndrome as well as aberrant origin of the right subclavian artery from the proximal descending thoracic aorta. In addition, microarray comparative genomic hybridization (aCGH) analysis confirmed a 102-kb deletion within chromosome band 9p24.2. These two findings have not been previously described with Berry syndrome.

Case Report

A 1-day-old female infant, weighing 3.69 kg and born at term to a 39-year-old, para 3 mother, presented with hypoxia within a few hours of birth. Pregnancy was complicated by diet-controlled gestational diabetes. The infant was born vaginally with Apgar scores of 8 at 1 minutes and 9 at 5 minutes. She was monitored in the nursery due to hypoglycemia and within a few hours of life was noted to have cyanosis without respiratory distress. Oxygen saturations were 80–90 % on room air with a nonresponsive hyperoxia test. Echocardiogram demonstrated an APW with IAA. Computed tomography (CT) angiography with three-dimensional (3D) reconstruction was performed to further delineate the cardiac anatomy. There was a large APW involving the entire length of the pulmonary trunk from immediately above both semilunar valves to the level

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of the pulmonary bifurcation (Fig. 1). Distal to the APW, at a location remote from the APW, the aorta was noted to give rise to the right pulmonary artery. The left pulmonary artery was noted to originate normally from the main pulmonary artery (Fig. 2). Imaging also showed a left-sided aortic arch with type A interruption (interruption distal to the left subclavian artery) and the descending aorta being fed by a large patent ductus arteriosus (PDA). CT angiography also confirmed an anomalous right subclavian artery arising from the descending aorta with passage posterior to the esophagus (Fig. 3).

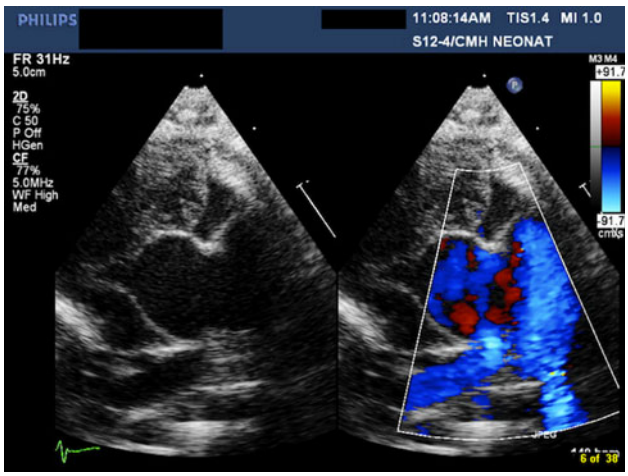

Fig. 1 Parasternal short-axis 2D and color Doppler echocardiogram demonstrating the APW

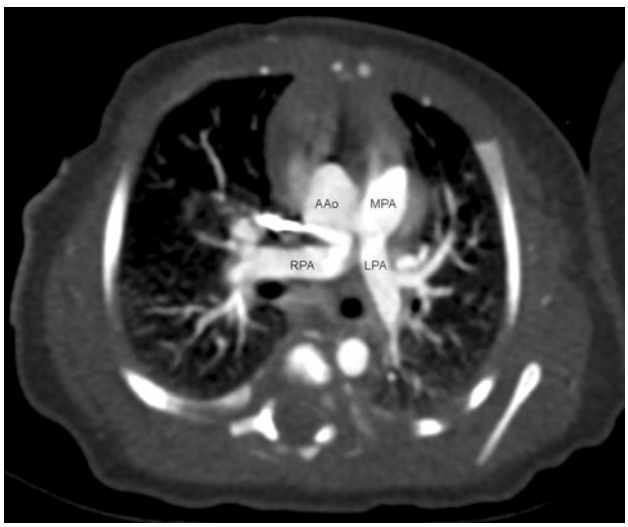

Fig. 2 CT angiography oblique axial multiplanar reformat demonstrates APW, right pulmonary artery arising from the aorta, and the left pulmonary artery arising from the main pulmonary artery. High-attenuation streak artifact from the intravenous contrast concentrated within the superior vena cava is also noted. *AAo* ascending aorta, *MPA* main pulmonary artery, *RPA* right pulmonary artery, *LPA* left pulmonary artery

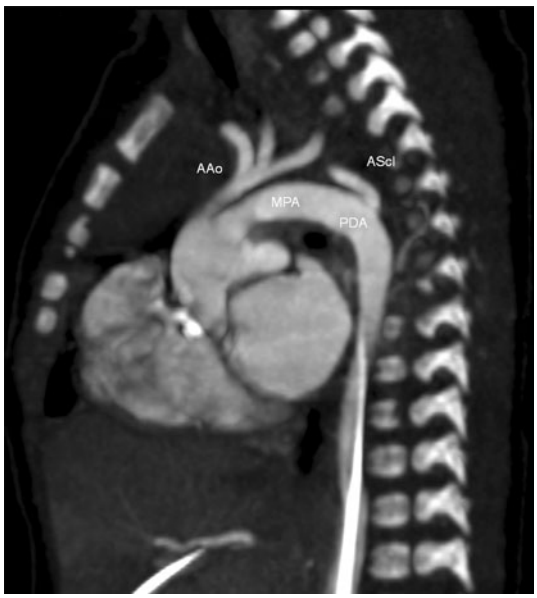

Fig. 3 CT angiography parasagital multiplanar reformat. *AAo* Ascending Aorta, *MPA* main pulmonary artery, *AScl* aberrant right subclavian artery

The patient was maintained on prostaglandin infusion in the intensive care nursery and, on day 7 of life, was taken to the operating room for definitive repair of her cardiac defects using cardiopulmonary bypass, profound hypothermia, and circulatory arrest. The IAA was repaired using a cryopreserved allograft and mobilization of the arch. The defects in the aorta and pulmonary artery (APW) were closed using allograft patches. The infant was extubated on postoperative day 5 and weaned from vasoactive medications by postoperative day 7. During her hospital stay, aCGH analysis was performed, which demonstrated a 102-kb deletion within chromosome band 9p24.2. Her mother was noted to have the same deletion without any confirmed cardiac defects.

Discussion

APW is a rare cardiac defect comprising 0.1–0.2 % of all congenital heart disease. Approximately 30–50 % of cases of APW have associated cardiac defects, the most common of which is IAA [5]. A classification system for APW and IAA based on the location of the defects has been described [3]. Type I APW describes a lesion midway between the semilunar valves and pulmonary artery bifurcation. Type II APW describes a distal defect with the distal portion near the pulmonary artery bifurcation. Type III APW encompasses aspects of both type I and type II defects as was seen in this neonate. IAA is classified by its relationship to the carotid and subclavian arteries. Type A interruption occurs

distal to the left subclavian artery; Type B (the most common) occurs between the left common carotid and left subclavian arteries; and Type C occurs proximal to the left common carotid artery. In those instances where both APW and IAA coexist, the most common type of arch interruption is type A as was seen in our patient [5]. This combination of defects can present a diagnostic challenge because early in an infant's course, the symptoms associated with IAA predominate, and the APW can be overlooked.

Very rarely, a combination of APW, IAA, intact ventricular septum, and PDA is associated with aortic origin of the right pulmonary artery and is termed "Berry syndrome" [1]. To date, approximately 25 cases of Berry syndrome have been described in the literature. Our patient had a unique, and not previously reported, finding of an aberrant right subclavian artery originating from the descending aorta.

One hypothesis that has been proposed for the combination of defects seen in Berry syndrome is impairment in blood flow to the aortic isthmus during fetal life as a result of the large communication between the aorta and pulmonary artery [4]. It has been postulated that the more remote the location of the right pulmonary artery from the APW, the greater the degree of "steal" and the greater the deprivation of the aortic arch. This hypothesis is, however, somewhat called into question because prenatal imaging of this defect in a single case report demonstrated right-to-left (pulmonary artery-to-aorta) shunting at the level of the APW [2].

Our patient also had the additional finding of an abnormal aCGH analysis. Although the clinical significance of this is unclear, we found no other reports in the literature where infants with Berry syndrome had genetic testing performed. Future aCGH testing of infants with this defect may help in identifying a genetic link, if one does indeed exist. APW and IAA type A are unrelated to the spectrum of defects seen in a neural crest abnormalities and 22q11 deletion, such as truncus arteriosus, IAA type B, and VSD. Although Berry syndrome does not seem to be pathogenetically related to a neural crest deformity, perhaps there are other plausible genetic mechanisms that could explain the unusual constellation of defects found in this syndrome. At this time, we are unable to verify this because aCGH testing was not reported in other case reports of Berry syndrome. Maternal diabetes has been implicated in a variety of fetal cardiac defects without clear understanding of the pathogenesis. It may be that higher maternal blood sugar and/or other derangements in the hormonal milieu may result in mutations like 9p24.2 deletion. However, this is less likely since the infant's mother also carries the same genetic mutation without a known cardiac phenotype.

Conclusion

Berry syndrome comprises a rare combination of heart defects that can be adequately imaged noninvasively and successfully repaired as a one-stage procedure during the neonatal period. Our patient was found to have a deletion within chromosome band 9p24.2, which has not been previously described with congenital heart disease. Although this relationship is unclear, we recommend aCGH analysis of all infants with Berry syndrome to identify possible genetic linkages.

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