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Identical Twins Discordant For Bicuspid Aortic

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ABSTRACT

Bicuspid aortic valve (BAV) is a congenital heart defect characterized by the presence of two aortic valve leaflets instead of the usual three. This structural anomaly affects approximately 1-2% of the general population and is linked to various complications, such as aortic stenosis, dilation, and aneurysm formation, due to turbulent blood flow through the valve. BAV is frequently inherited, with studies suggesting an autosomal dominant pattern with incomplete penetrance, indicating that genetic predisposition alone does not guarantee its development. In fact, despite the hereditary basis of BAV, cases have emerged showing discordance in BAV phenotypes among monozygotic twins, including monochorionic twins, where concordance rates are estimated at around 20%. These findings suggest that, in addition to genetic factors, epigenetic and environmental influences during prenatal development may play crucial roles in BAV manifestation. This discordance among identical twins highlights the potential impact of intrauterine conditions, such as oxygen levels and other environmental exposures, that may influence the phenotypic expression of BAV.

We present a case of phenotypic discordance in identical 66- year-old male twins. The first twin was diagnosed with severe aortic stenosis and a BAV, accompanied by a thoracic aortic aneurysm. He underwent successful transcatheter aortic valve replacement (TAVR) and aortic grafting. His identical twin brother was identified to have aortic valve with no significant aortic abnormalities and only mild pulmonary artery dilatation.

The findings from this case study underscore the complexity of bicuspid aortic valve (BAV) inheritance, indicating an autosomal dominant pattern with incomplete penetrance. The discordance observed among identical twins highlights the significant roles of epigenetic and environmental factors in the manifestation of this condition. While genes such as NOTCH1, GATA5, and FBN1 are implicated in BAV, their expression may be modulated by various external conditions during development. Factors like maternal health, nutritional status, and exposure to environmental toxins can influence epigenetic modifications, resulting in differences in gene expression that affect cardiac morphology. Additionally, prenatal conditions unique to monochorionic twins, including twin-to-twin transfusion syndrome, can further complicate phenotypic expression. This interplay between genetic predispositions and environmental influences emphasizes the need for a comprehensive approach to understanding the etiology of BAV and other congenital heart defects.

This case emphasizes the need for further research into the genetic, environmental, and epigenetic factors influencing BAV development. Understanding these factors may improve genetic counseling, early diagnosis, and intervention strategies for BAV.

Keywords: Environmental influences; Epigenetic Discordant; Identical twins; Bav; Case reports

INTRODUCTION

Bicuspid aortic valve (BAV) represents a congenital heart valve anomaly characterized by an aortic valve with two leaflets rather than the typical three. In approximately 80% of cases, leaflet fusion occurs between the right and left coronary cusps [1,2]. This structural defect results in high-velocity, turbulent blood flow that imposes stress on the aortic wall, leading to complications such as aortic stenosis and dilation [1,2]. BAV is the most prevalent congenital valve defect, affecting an estimated 1-2% of the general population [3], with a notably higher incidence among identical twins. However, the concordance rate in identical twins is low, with both twins affected in only around 20% of cases, suggesting significant contributions from epigenetic and environmental influences [4,5,6]. Such hemodynamic changes associated with BAV lead to complications in over one-third of affected individuals [7].

Although the genetic underpinnings of BAV are not fully elucidated, the defect is believed to exhibit strong heritability [8,9]. Given this genetic association, current guidelines recommend screening first-degree relatives of individuals diagnosed with BAV [10]. Nevertheless, discordant BAV phenotypes among identical twins underscore the likelihood of influences beyond genetic factors alone. This case study of identical twins presenting with discordant aortic valve morphology provides valuable insights into the interplay of genetic and external factors in the pathogenesis of BAV [4,5,6].

CASE PRESENTATION

A 66-year-old male with a history of hypertension (HTN) and a family history of coronary artery disease (CAD) was referred by his primary care physician for evaluation of a thoracic aneurysm noted on a CT chest scan conducted during lung cancer screening. The patient reported no apparent cardiac symptoms such as chest pain, palpitation, exerting dizziness, edema, and syncope. His height was 167 cm, and his weight was 72.5 Kg. Physical exam revealed grade 5/6 mid systolic murmur at the right upper sternal border. He described that his twin identical brother also has had heart murmurs since birth.

An electrocardiogram (EKG) showed bradycardia with a heart rate of 50 beats per minute and a right bundle branch block (RBBB). An echocardiography discovered severe aortic stenosis with dilated left ventricle but without left ventricle hypertrophy. The valve area was reduced to 0.35 cm2. The peak gradient across the aortic valve was 76 mmHg with a mean gradient of 53 mmHg, and the velocity was 4.4 m/s. A chest CT revealed an aneurysm of the thoracic aorta with a diameter of 4.6 cm. A cardiac stress test was conducted, and he completed 4 minutes of treadmill exercise, achieving 4.6 METS, and discovered mild to moderate anterolateral ischemia.

Cardiac catheterization confirmed severe aortic stenosis and the presence of a bicuspid aortic valve, leading to a referral for transcatheter aortic valve replacement (TAVR). The patient underwent a surgical replacement of the aortic valve with a 27mm INSPIRIS pericardial tissue valve, and the ascending aorta using a 28mm Hemashield Platinum Aortic Branch graft. His postoperative follow-up CT angiography showed no complications; the aortic arch and descending thoracic aorta remained patent without aneurysmal dilation or intramural dissection flaps. He reported discomfort, pain, and fatigue in both legs after walking some distance, which improved with rest. Follow-up EKG showed no significant changes, except for newly diagnosed atrial fibrillation in which the patient started on amiodarone.

Followingly, his identical twin brother, a 66-year-old male with a history of HTN and hyperlipidemia, presented at the office for a concierge visit. He complained of chest pain exacerbated by exercise, though previous stress tests were normal. His blood test and EKG did not indicate any specific problem. A transthoracic echocardiography revealed pulmonary artery dilation, but the aortic valve was trileaflet without stenosis, and the aortic root did not have any abnormality with a diameter of 3.9 cm, which is within the normal limit.

DISCUSSION

Monozygotic (MZ) twins are considered a useful model to demonstrate the interaction between environmental and genetic factors in the etiology of many complex traits. factors contributing to discordance in BAV Involves de novo somatic mutations, Incomplete penetrance, epigenetic changes, Microenvironmental factors, and placental blood flow variances (with inequalities in oxygen and nutrition delivery [11,12].

There are several hypotheses of how BAV is inherited. A prospective study with first-degree relatives suggests its inheritance as autosomal dominant with incomplete penetrance [13]. Genes that are suggested to be related to BAV include NOTCH19, GATA5 [14,15], and FBN1 [16]. Among the suggested genes, a study with a mouse model has identified that targeted deletion of GATA5 leads to partially penetrant BAV with fusion of the right and noncoronary leaflets [17]. Regarding this gene, there is a report about sporadic cases of dyssynchronous gene transcription through families with BAV [16].

However, there is no confirmed mechanism that explains the aspect of congenital heart defect incidence in twins. There is a cohort study of 41,525 twins in Denmark, which concluded that the incidence increased by 63% in twins compared to singletons, but this article did not include identical twins in its cohort [18]. A case series study has reported two cases of discordance of BAV phenotype between identical twins [19].

Further study to find factors in the embryonic process may be valid. A retrospective study with a longitudinal comparison of cardiac obstetric ultrasound between 356 twin pairs throughout gestation has suggested twin-to-twin transfusion syndrome recipients during gestation as a potential risk factor for congenital valve dysplasia Although the cases do not include BAV, the authors explained that oxygenation may contribute to the discordance during valve development.

A Clinical Case Series was done to analyze genetic differences between 2 pairs of monozygotic twins with discordant aortic valve morphology. This study used whole-exome sequencing and targeted gene sequencing to detect Genetic coding variations between monozygotic twins and revealed that identified no pathogenic sequence changes between the twins in each pair [20]

The study from BMC Medicine examined the epigenetic and environmental influences on monozygotic twins discordant for bicuspid aortic valve (BAV). It found significant differences in DNA methylation between the twins, with one pair exhibiting 330 differentially methylated sites, 27 of which were common between both pairs analyzed. Remarkably, 83% of these methylation changes were not inherited, indicating that environmental factors-such as maternal nutrition, toxin exposure, and other external stresses-play a crucial role in shaping phenotypic outcomes.

CONCLUSION

In conclusion, this case study of identical twins discordant for bicuspid aortic valve (BAV) illustrates the intricate interplay between genetic, epigenetic, and environmental factors in the manifestation of BAV. Although BAV inheritance is believed to follow an autosomal dominant pattern with incomplete penetrance, the low concordance observed among identical twins underscores the role of non-genetic influences. Epigenetic modifications, which may be affected by differential intrauterine conditions and phenomena such as twin-to-twin transfusion syndrome, can alter gene expression, contributing to the phenotypic variability of BAV. Environmental factors, including variations in maternal health, nutritional status, and oxygenation levels during gestation, likely further influence these epigenetic changes, complicating the developmental pathways that lead to BAV. Understanding these multifactorial interactions is essential for advancing personalized approaches to screening, prevention, and management of BAV and other congenital heart diseases.

DISCLOSURES

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