Surprise, Surprise: Idiopathic, Isolated Complete Atrio-Ventricular Block May Be Heritable

Running title: Cannon et al.; Heritability of idiopathic, isolated CAVB

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Baruteau and colleagues present findings that further the potential for a genetic basis for non-immune isolated atrio-ventricular block\textsuperscript{1}. Their observations warrant further consideration in the evaluation and management of patients with no definitive cause of their cardiac conduction defect.

Congenital complete AV block (CAVB) affects about 1 in 20,000 live-born infants\textsuperscript{2} and is associated commonly with an immune related cause related to maternal collagen vascular disease or structural cardiac disease.\textsuperscript{3} Other causes of CAVB have been described including infections, myopathies, and genetic disorders including Hunter and Hurler syndromes. Still, the specific cause for CAVB remains elusive for a significant number of patients raising the possibility that a portion of idiopathic CAVB stems from CAVB-susceptibility genes. Currently, mutations in transcription factors and cardiac channels yield electrocardiographic phenotypes that include cardiac conduction abnormalities.

For example, patients with NKX2.5 mutations can have cardiac conduction defects, cardiomyopathy, and atrial septal defects.\textsuperscript{4} Long QT syndrome has also been associated with both 2:1 atrio-ventricular block as well as CAVB, but this is usually in the presence of overt QT prolongation on the ECG.\textsuperscript{5} Mutations in the SCN5A-encoded Nav1.5 sodium channel has an ever expansive breadth of channelopathic/cardiomyopathic phenotypes including type 3 long QT syndrome, type 1 Brugada syndrome, dilated cardiomyopathy as well as atrial standstill and conduction disturbances.\textsuperscript{6}

Among patients with idiopathic CAVB, the electrophysiologic phenotype may extend beyond the AV node. In Baruteau’s cohort, a wide QRS complex was noted in almost 10\% of patients with childhood AVB and in nearly one-third of patients with congenital CAVB which is extremely high when compared to patients with immune-mediated CAVB where a wide QRS
complex is relatively rare and is a Class I indication for a pacemaker. This high percentage of wide QRS complexes suggests a more diffuse disease of the conduction system rather than an effect on just the AV node. In addition, this defect may also affect conduction velocity as is evidenced by a prolonged P wave as well as QRS complex seen in the parents of affected individuals compared to controls. Although the QT and corrected QT intervals measured within normal limits, both intervals were statistically longer in parents compared to the control population. Although there is an effect on conduction velocity, there did not seem to be an effect on spontaneous depolarization as the heart rates were almost identical in the two groups.

It is interesting that more than two-thirds of their patients with incomplete AVB progressed to having CAVB suggesting a progressive mode of damage to the AV node, not just an underlying static channelopathy. However this progression seems to exclusively involve the conduction system as no patient died or developed dilated cardiomyopathy with a median follow-up of 11 years.

There is likely a complex interaction between multiple genes in genetically mediated CAVB as the ECG phenotypes were different in children and their parents. Since virtually all cardiac channelopathies and cardiomyopathies are underscored by marked genetic and phenotypic heterogeneity, incomplete penetrance, and variable expressivity, we can anticipate the same story line for genetically-mediated CAVB not to mention the likely contribution of “modifier genes” for the patients who progress from incomplete to complete AVB. Further, compound heterozygosity and the “two-hit” phenomenon may underlie some CAVB as inferred from their observation that cardiac conduction impairment (but not complete AV block) was noted in both parents in 30% of the cohort.

However, before proceeding with genetic testing of known channelopathy- or
cardiomyopathy-associated genes as intimated by the authors, caution and restraint are probably the “words of the day”. The recent 2011 guidelines suggested a “may be considered” recommendation regarding genetic testing for isolated/familial cardiac conduction disease and urged careful interpretation of the genetic test results.\(^8\) Currently, the anticipated yield of bona fide \(SCN5A\) defects for otherwise idiopathic CAVB is unknown while the potential false positive rate is around 2% in Caucasians and 4-5% in non-Caucasians.

In addition, a major point lacking in this study is the evaluation of siblings. If there is truly a familial process, it would stand to reason that many of the siblings would be affected with conduction system disturbances or even unrecognized CAVB. As there are many causes of conduction system disturbances in adults, including acquired coronary artery disease, it is important to truly document that the CAVB is a heritable condition and not related to exogenous environmental factors.

This study certainly has implications in the familial evaluation of infants and young children with progressive or complete AV block. Evaluation of the parents may reveal an underlying conduction defect. Electrocardiograms on siblings of affected individuals may also be indicated to reveal conduction disturbances with no overt symptoms. If these conduction disturbances are present, they may need to be followed for progression to higher grades of AV block over time. Evaluation of multiple cohorts in families may lead to the identification of new genes responsible for cardiac conduction defects, which also may be responsible for other channelopathies. The study also may have implications for affected individuals, particularly those stemming from \(SCN5A\) defects. These patients may need to be advised to avoid medications that are contraindicated in Brugada Syndrome, Long QT Syndrome, or both.

As with most studies, the authors have suggested rightly that further studies need to be
conducted to determine the true ramifications of the findings in this study.

**Conflict of Interest Disclosures:** BCC is a consultant for Medtronic and St. Jude Medical. MJA is a consultant for Biotronik, Boston Scientific, Medtronic, St. Jude Medical, and Transgenomic. Intellectual property derived from MJA’s research program resulted in license agreements in 2004 between Mayo Clinic Health Solutions (formerly Mayo Medical Ventures) and PGxHealth (formerly Genaissance Pharmaceuticals and now Transgenomic) with respect to their FAMILION-LQTS and FAMILION-CPVT genetic tests.

**References:**


