B aruteau and colleagues present findings that further the potential for a genetic basis for nonimmune isolated atrioventricular (AV) block. Their observations warrant further consideration in the evaluation and management of patients with no definitive cause of their cardiac conduction defect.

**Editorial**

**Surprise, Surprise**

*Idiopathic, Isolated Complete Atrioventricular Block May Be Heritable*

Bryan C. Cannon, MD; Michael J. Ackerman, MD, PhD

Congenital complete AV block (CAVB) affects ∼1 in 20,000 live-born infants and is commonly associated with an immune-related cause associated with maternal collagen vascular disease or structural cardiac disease. Other causes of CAVB have been described, including infections, myopathies, and genetic disorders such as the Hunter and Hurler syndromes. Still, the specific cause of 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. Long-QT syndrome has also been associated with both 2:1 AV block ad CAVB, but this is usually in the presence of overt QT prolongation on the ECG. Mutations in the SCN5A-encoded Nav1.5 sodium channel have an ever-expansive breadth of channelopathic/cardiomyopathic phenotypes, including type 3 long-QT syndrome, type 1 Brugada syndrome, dilated cardiomyopathy, and atrial standstill and conduction disturbances.

Among patients with idiopathic CAVB, the electrophysiological phenotype may extend beyond the AV node. In the Baruteau et al cohort, a wide QRS complex was noted in almost 10% of patients with childhood AV block and in nearly one third of patients with congenital CAVB, which is extremely high compared with patients with immune-mediated CAVB in which 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 affect conduction velocity, as is evidenced by a prolonged P wave and QRS complex seen in the parents of affected individuals compared with control subjects. Although the QT and corrected QT intervals measured within normal limits, both intervals were statistically longer in parents compared with the control population. Although there is an effect on conduction velocity, there did not seem to be an effect on spontaneous depolarization because the heart rates were almost identical in the 2 groups.

It is interesting that more than two thirds of their patients with incomplete AV block 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 involve the conduction system exclusively because no patient died or developed dilated cardiomyopathy during a median follow-up of 11 years.

There is likely a complex interaction between multiple genes in genetically mediated CAVB because the ECG phenotypes were different in children and their parents. Because 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 in the patients who progress from incomplete to complete AV block. Furthermore, compound heterozygosity and the 2-hit phenomenon may underlie some CAVB, because we can infer 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 initiated by the authors, caution and restraint are probably the words of the day. The recent 2011 guidelines suggested a “may be considered” recommendation concerning genetic testing for isolated/familial cardiac conduction disease and urged careful interpretation of the genetic test results. Currently, the anticipated yield of bona fide SCN5A defects for otherwise idiopathic CAVB is unknown, whereas the potential false-positive rate is ∼2% in whites and 4% to 5% in nonwhites.

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. Because 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 is 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. ECGs 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 up 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 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 rightly suggested that further studies need to be conducted to determine the true ramifications of the findings of this study.

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

References

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