Investigating the Relationship Between Heart Rate, QT, and QTc in Alternating Hemiplegia of Childhood and Other *ATP1A3*-Associated Phenotypes

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Background: Alternating hemiplegia of childhood (AHC) is a rare condition most frequently caused by mutations in *ATP1A3,* encoding for the alpha-3 subunit of Na^+/K^+-ATPase, and D801N is the most common variant. Individuals with ATP1A3-D801N have shorter corrected QT (QTc) than those with other variants and can experience ventricular arrhythmias following bradycardia; however, the mechanism of why this occurs is unknown.

Methods: In this retrospective observational study, patients seen for evaluation of AHC at Duke University Medical Center were categorized by genotype: ATP1A3-D801N, ATP1A3 non-D801N single nucleotide variant, *ATP1A3* loss-of-function variant, and genotype negative. A cohort of matched healthy children was also compiled. We collected average heart rate, QT, and QTc measurements over 5-minute intervals from Holter recordings using HScribe™ software and conducted manual blinded validation to ensure accuracy. We then used linear regression to investigate the relationship between heart rate, QT, and QTc.

Results: The cohort consisted of 44 patients with *ATP1A3*-related phenotypes with 81 total Holter recordings (52.27% female; mean age at first Holter 8.04 years), compared to 36 healthy individuals with 57 total Holter recordings (52.78% female; mean age at first Holter 9.84 years). Patients with ATP1A3-D801N showed diminished prolongation of QT with decreasing heart rate, manifested as a reduced mean slope for heart rate vs QT compared to healthy (-0.85 ± 0.46 vs -1.52 ± 0.42, $p<0.0001$). This blunted QT response resulted in paradoxical shortening of QTc at lower heart rate, demonstrated by an increased mean slope for heart rate vs QTc compared to healthy (0.80 ± 0.51 vs 0.22 ± 0.43, $p<0.0001$). Further, patients with *ATP1A3*-related phenotypes and very short baseline QTc showed increased shortening of QT and QTc at lower heart rate compared to those with normal QTc ($p=0.0025$ and $p=0.0013$, respectively).

Conclusions: Children with AHC and ATP1A3-D801N demonstrate a paradoxical shortening of QT and QTc with slowing of heart rate. The impaired prolongation of QT and resultant further shortening of QTc increase the risk of arrhythmia. We put this forward as a novel mechanism of sudden cardiac arrest in patients with *ATP1A3* mutations.