Acquired Post Partum Bradycardia Associated with Mutations in the HCN4 Cardiac Ion Channel

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Background: The hyperpolarization-activated nucleotide-gated channel-HCN4 plays a major role in the diastolic depolarization of sinus node cells. Mutant HCN4 channels have been found to be associated with inherited sinus bradycardia(SB). We sought to investigate the clinical and genetic features of patients developing post partum SB.

Methods: Clinical evaluation included 24- hr ECG holter recording and echocardiogram at baseline (immediate post partum period) and 24- hr ECG holter and exercise testing 6-12 month later . Genetic analysis included segregation analysis and direct sequencing of all exons encoding HCN4.

Results: Between 2008- 2010, 15 women were referred to arrhythmia service due to unexplained SB with an average heart rate (HR) of 42± 5 on ECG after uneventful pregnancy and delivery of a healthy child. All were mildly symptomatic, hemodynamically stable and recovered gradually without any therapy. None of them were known to have bradycardia before or during pregnancy. All but one had a negative family history of bradycardia. All had a normal echocardiogram. Holter recording demonstrated a minimum HR of 40± 4, average HR of 54±9 and maximal HR of 96± 17. Three patients (20%) were found to have missense mutation in HCN4. Two had a newly described M1113V mutation and one had an A485V mutation found previously by our group to cause an HCN4 loss of function. Six patients were followed up (avg: 7± 2 months). None of them were symptomatic. Average, maximal and minimal HR respectively increased on holter recording (72± 9 and 134± 24 vs. baseline; $p< 0.05$ and 48± 7 vs. baseline; $p= 0.2$). Exercise testing (n=4) demonstrated normal chronotropic competence.

Conclusions: We describe a new clinical entity of post partum SB. These patients had benign clinical course with rapid recovery Around 20% were found to carry HCN4 mutations., Post partum hormonal changes may accentuate predisposing factors such as HCN4 loss of function mutations resulting in SB.