LETTER TO THE EDITOR

Investigating genetic variation of adrenergic receptors in familial stress cardiomyopathy (apical ballooning syndrome)

To the Editor,

In their recently published article, Sharkey et al. [1] genotyped three adrenergic receptor polymorphisms in a cohort of 41 patients with stress cardiomyopathy (SC). This idiopathic but reversible disorder, also known as takotsubo cardiomyopathy and apical ballooning syndrome, typically occurs in postmenopausal women, presenting with ischemia-like chest pain, transient ECG changes, and minor cardiac biomarker elevation following acute emotional or physical stress. Angiography of SC patients demonstrates unobstructed coronary arteries, while ventriculography shows hyperkinesis of the basal myocardium and hypokinesis of the apical and/or mid-ventricular wall extending beyond the territory of a single coronary artery [2]. Sharkey et al. investigated functional polymorphisms of B1 and alpha 2c adrenergic receptors, previously implicated in increased activation of the sympathetic nervous system, but found no significant differences in polymorphism frequencies between SC patients and controls. However, a genetic basis for the disorder is suggested by familial cases [3,4], and a fundamental defect in adrenergic signaling remains one of the most compelling pathogenic hypotheses [5,6], providing the rationale for our comprehensive mutational analysis of adrenoreceptor genes in a rare case of familial SC [4].

We targeted the genes encoding the B1 (ADRB1), B2 (ADRB2), and alpha 2c (ADRA2C) adrenergic receptors, which harbor functional variants modulating cardiac response to catecholamines. Indeed, Zaroff et al. demonstrated an association between polymorphisms within these adrenoreceptors and cardiac dysfunction attributed to post-subarachnoid hemorrhage (SAH)-induced catecholamine surge [5]. In particular, the Arg-389 ADRB1 and ADRA2C del322–325 polymorphisms, linked to enhanced cardiac catecholamine sensitivity and impaired regulation of norepinephrine release, respectively, were independently and synergistically associated with cardiac injury. Notably, the reversible regional left ventricular dysfunction seen in SAH patients is phenotypically similar to SC.

For our study we included ADRB2, in addition to ADRB1 and ADRA2C, based on evidence from animal investigations. Higher concentrations of B-adrenoreceptors were found in the apical versus basal myocardium in canine hearts, indicating that the apex may be more sensitive to circulating catecholamines. Furthermore, over-expression of human B2-adrenergic receptors in mice subject to supra-physiological epinephrine levels had a negative inotropic effect on cardiomyocytes. These observations led to the hypothesis that during times of stress, when epinephrine is the main circulating catecholamine, regional differences in epinephrine sensitive B2-receptors could explain the myocardial response to catecholamine surge seen in SC [6]. Thus, we postulated that mutation of ADRB2 could accentuate vulnerability of the heart to adrenergic stress.

A genomic DNA sample was obtained from a previously reported 44-year-old female with familial SC [4], which recurred one year later after a second episode of extreme emotional stress. Written informed consent was provided under a protocol approved by the Mayo Clinic Institutional Review Board. To sequence the targeted genes, primer pairs were designed for polymerase chain reaction amplification of the entire coding regions of the single exon genes ADRB1 (2862 bp), ADRB2 (2033 bp) and ADRA2C (1952 bp). Homozygosity for the more common alleles of established functional polymorphisms was found (ADRA2C wt/wt, ADRB1 389 Arg/Arg, ADRB1 49 Ser/Ser). Moreover, comprehensive DNA sequence analysis of these adrenergic receptor genes revealed no mutations in our familial SC case. While a molecular defect in adrenergic signaling remains a plausible pathogenic mechanism, our data together with the findings of Sharkey et al. indicate that the underpinnings of SC are not likely based on genetic variation in adrenergic receptors.

References


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