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LETTERS

RESEARCH LETTER

Polycystic Ovarian Syndrome and Brugada Syndrome Phenotype in Women

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Brugada syndrome (BrS) is a potentially inherited cardiac channelopathy that exhibits strong male predominance.[1] Testosterone contributes to increased BrS penetrance and expressivity in men, but whether androgen excess modulates BrS-associated expressivity in women remains undefined. We examined whether polycystic ovary syndrome (PCOS) and other hyperandrogenic disorders (eg, idiopathic hirsutism, congenital adrenal hyperplasia, Cushing disease, androgen-secreting tumors)[2] are associated with the following: 1) prevalence of a type 1 Brugada electrocardiogram (ECG) pattern; and 2) clinical outcomes among consecutive women referred to a North American Genetic Heart Rhythm Clinic.

In this single-center retrospective study (approved by the Mayo Clinic Institutional Review Board), we reviewed all women aged >16 years evaluated for BrS at the Windland Smith Rice Genetic Heart Rhythm Clinic between January 2000 and October 2025. Demographic, clinical, ECG, genetic, and therapeutic data were extracted from the medical record. Hyperandrogenic diagnoses were ascertained from endocrinology/gynecology documentation; available androgen testing and PCOS-directed therapies at the time of symptoms and at BrS evaluation were recorded when present.

Of 190 patients evaluated for BrS, 64 (33%) were women (mean age 37 ± 19 years). Among them, 32 (50%) had a type 1 Brugada ECG pattern (31 spontaneous and 1 drug induced), and 57 (89%) had a pathogenic/likely pathogenic variant in the *SCN5A*-encoded Nav1.5 cardiac sodium channel (**Table 1**).

Hyperandrogenic conditions were identified in 7 (11%) of 64 women, all with PCOS. Where available, androgen levels were elevated (3 of 7). The prevalence of the type 1 Brugada ECG pattern did not differ between women with and without PCOS (4 of 7 [57%] vs 28 of 57 [49%]; $P = 0.7$). Although arrhythmogenic syncope was only noted in women without PCOS (9 of 57 [16%] vs 0 of 7 [0%]; $P = 0.3$), there was no difference in the number of women with and without PCOS who received an implantable cardioverter-defibrillator (ICD) (3 of 7 [43%] vs 12 of 57 [21%]; $P = 0.3$).

Of note, women with PCOS were more likely to have a history of vasovagal syncope/pre-syncope (4 of 7 [57%] vs 5 of 57 [9%]; $P = 0.008$), with 3 (75%) of 4 receiving a primary prevention ICD before their BrS-focused evaluation. In contrast, none of the non-PCOS women with suspected vasovagal syncope/presyncope received an ICD. To date, no patient with PCOS has experienced appropriate ICD therapy. Only 1 of 7 women with PCOS was receiving PCOS-directed therapy at the time of their index BrS diagnosis (before presentation to the Genetic Heart Rhythm Clinic), and none of the women with vasovagal syn-

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TABLE 1 Clinical Characteristics of Women With Brugada Syndrome

	PCOS (n = 7)	Non-PCOS (n = 57)	*P* Value
Age at evaluation, yrs	30 ± 9	45 ± 17	0.02[a]
White race	7 (100)	51 (89)	0.99[b]
Arrhythmic syncope	0 (0)	9 (16)	0.58[b]
Vasovagal syncope/presyncope	4 (57)	5 (9)	0.008[b]
Type 1 Brugada ECG pattern	4 (57)	28 (49)	0.72[b]
P/LP variant in *SCN5A*[c]	6 (100)	51 (94)	0.99[b]
Non-missense mutation[d]	5	29	
Missense mutation	1	21	
Compound heterozygote missense mutation	0	1	
ICD implantation	3 (43)	12 (21)	0.34[b]
Indication for ICD implantation			
Cardiac arrest	0	4	
Syncope	2	2	
Syncope with positive EP study	0	1	
Syncope with negative EP study	1	1	
Concomitant need for pacing	0	1	
Family history of sudden death	0	1	
Patient preference	0	2	
Follow-up after ICD implantation, yrs	2.4 ± 1.3	9.2 ± 5.9	0.003[a]
Appropriate ICD therapies in follow-up[e]	0 (0)	3 (5)	0.99[b]
Pacemaker implantation	0 (0)	2 (4)	0.99[b]
PCOS-directed therapy at time of presentation to the Genetic Heart Rhythm Clinic	4 (57)	NA	NA
Clinic evaluation			
Metformin	2 (29)		
Oral progesterone/combined contraceptive	2 (29)		
Spironolactone	1 (14)		

Values are mean ± SD or n (%). [a]Variables compared by using Welch's two-sample *t* test. [b]Variables compared by using Fisher exact test. [c]One patient in the polycystic ovarian syndrome (PCOS) group and 3 patients in the non-PCOS group did not pursue genetic testing. [d]Non-missense mutations (nonsense, frameshift, in-frame deletion, canonical [±2] splice site, and copy number variants) are associated with more severe arrhythmic manifestations than missense mutations in Brugada syndrome. [e]A total of 3.02 appropriate implantable cardioverter-defibrillator (ICD) therapies per 100 person-years of follow-up in non-PCOS patients with ICD vs 0 appropriate ICD therapies per 100 person-years of follow-up in PCOS patients with ICD (two-sided $P = 1.0$).

ECG = electrocardiogram; EP = electrophysiology; NA = not applicable; P/LP = pathogenic/likely pathogenic.

cope/presyncope was receiving PCOS-directed therapy at the time of the index events.

The prevalence of PCOS in this cohort (approximately 11%) seems similar to that in the general US population.[3] The frequency of a type 1 Brugada ECG pattern was similar in women with and without PCOS, but vasovagal symptoms led to frequent ICD implantation in women with PCOS.

BrS expression and arrhythmic risk depend on the balance of inward (INa, ICa-L) and outward (Ito, IKr, IKs) currents across the right ventricular epicardium. Testosterone contributes to the higher prevalence and severity of BrS in men through inhibition of ICa-L and enhancement of Ito/IKr/IKs currents.[4] Although emergence of a Brugada ECG pattern has been reported in a female-to-male transgender individual receiving testosterone,[5] our findings do not show a clear signal that the degree of endogenous androgen excess typically associated with PCOS meaningfully modulates the BrS phenotype in women.

Vasovagal syncope or presyncope occurred in 14% of all women with BrS but was overrepresented in those with PCOS. Autonomic dysfunction linked to PCOS or heightened symptom-driven evaluation may explain this finding. None of the PCOS patients reported arrhythmic syncope, yet 3 of 7 received primary prevention ICDs. None of the PCOS patients who received an ICD have experienced appropriate ICD therapies to date. These findings emphasize the importance of careful risk stratification and adherence to guideline-directed indications for an ICD in women with BrS.

Limitations of this study include small sample size (with limited power to detect modest between-group differences and high risk of type II error), retrospective design, referral and potential survivor bias, nonsystematic hormonal assessment, possible phenotype modulation by PCOS therapies, and shorter post-ICD follow-up assessment in the PCOS group. The high proportion of *SCN5A*-positive cases likely reflects referral bias.

In summary, in this single-center cohort, PCOS was not overrepresented among women evaluated for BrS and was not associated with a higher prevalence of a type 1 Brugada ECG pattern or arrhythmic syncope; these findings are hypothesis generating, however, given the small sample size. Nonetheless, careful evaluation remains warranted, as erroneous interpretation of vasovagal symptoms may lead to unnecessary ICD implantation in low-risk women with BrS, placing them at risk of device-related complications.

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