

CASE REPORT

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In a case of female-to-male sex reassignment, testosterone therapy switches on an underlying Brugada

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Abstract

Background: The Brugada syndrome, diagnosed by a typical electrocardiographic pattern, is a genetic condition characterised by an increased risk of potentially lethal ventricular arrhythmias and sudden cardiac death. Even if its pathophysiological mechanism is unknown, its prevalence in male suggested a possible hormonal involvement.

Case presentation: In this case involving a woman who underwent a female-to-male sex reassignment, we documented that testosterone administration was able to switch on and, when stopped, to switch off a latent pattern of Brugada.

Conclusions: Our observation strongly supports a possible involvement of testosterone in the ECG manifestation of Brugada syndrome even if the general low prevalence of the Brugada syndrome does not support to screen every female-to-male sex reassignment.

Keywords: Brugada syndrome, Testosterone, Sex change

Introduction

Sex change is a dramatic and controversial procedure that allows anatomical, legal, and psychosocial adaptations to another gender. Hormonal treatments are administered as a part of the procedures for sex reassignment and, in a female-to-male reassignment, include a testosterone preparation and a possible testosterone maintenance [1]. In theory, the hormonal changes over time could alter the cardiovascular risk profile related to the different gender, even if it appears to be rather safe in the short and medium term, as a study seems to suggest [2]. Unfortunately, there are no data in the literature on the possibility that a latent pathological phenotype can be, eventually, switched on by testosterone therapy. In this regard, we

know that the Brugada syndrome, recognised since 1992, occurs in males about 8–10 times more than in women [3]; thus, a possible hormonal involvement might play a role. Currently, the diagnosis is based on the detection of a typical electrocardiographic pattern (type 1). Furthermore, there are twelve known genes potentially responsible for the condition [4], and all genotypes correlate with alterations of cardiac action potential determined by a decrease in inward sodium or calcium currents, or an increase in outward potassium currents. Although there are some publications [4, 5] connecting the hormonal influence with the evidence of arrhythmias and Brugada syndrome, here we present a case report that, for the first time, supports a direct connection between androgen therapy and the Brugada pattern switch-on. This case is about a young woman who underwent a sex change and, after she started a testosterone-based therapy, she manifested a typical Brugada pattern on ECG.

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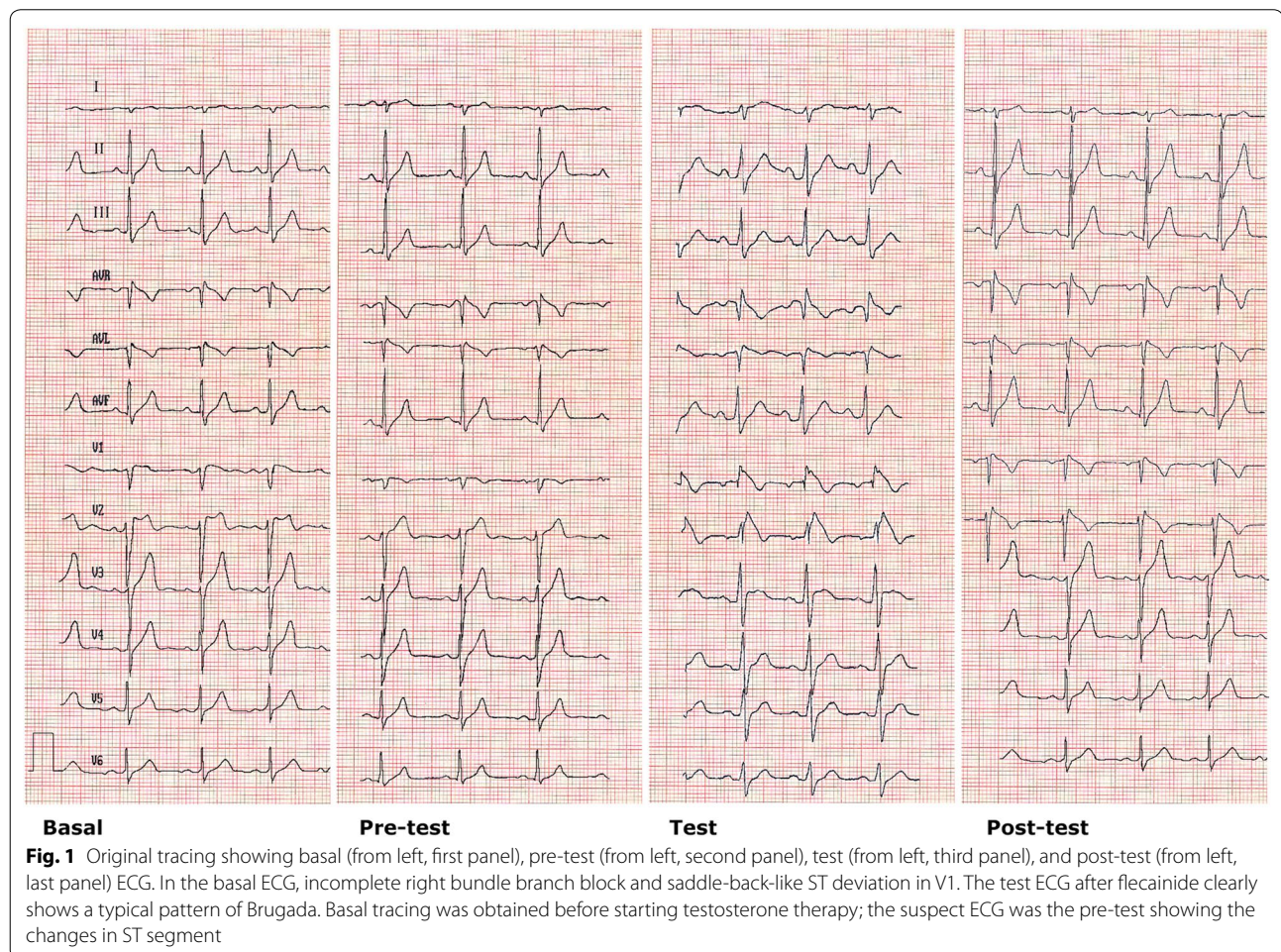
Case

In a 30-year-old woman admitted to gynaecology for a sex change, an ECG was obtained and a Brugada syndrome was suspected. Previous ECGs were normal. She took testosterone for about a year. In a subsequent ECG performed during a routine cardiological visit, it was evident a 1-mm ST segment elevation in V2 lead. She was, therefore, referred to our Center of Genetic Heart Disease and Arrhythmias. She had not have family history of sudden death and she denied syncope in her personal history, but palpitations were reported when assuming testosterone. A dosage of plasma testosterone and a 24-hour Holter ECG were obtained. Thereafter, a flecainide test was performed unmasking a typical ECG pattern of Brugada (Fig. 1). Genetic tests were negative for mutations related to SCN5A [6], the gene coding for the α -subunit of the most abundant sodium channel in the heart; after momentary suspension of testosterone, the ECG no longer showed a Brugada pattern. When the hormone was reintroduced, the Brugada pattern reappeared on the ECG along with the same episodes of palpitation, while

major arrhythmias were never documented. Original ambulatory ECG tracings done during the follow-up are shown in Fig. 2.

Discussion

The pathophysiological mechanism for Brugada syndrome is essentially unknown. The debate whether Brugada syndrome is linked to heart depolarisation or repolarisation is still open. The identification of mutations in the genes encoding the sodium channels, suggests a disturbance of the depolarisation; for a long time, it was thought that at the base of the pathophysiological mechanism was the impaired depolarisation localised in the right ventricular outflow tract level, due to a mismatch between the transient outward potassium current I_{to} and the sodium current depolarising (I_{Na}). The right ventricular outflow tract is the area considered as the arrhythmogenic substrate of the disease because it presents different characteristics of the distribution of ion channels, compared to the other parts of the heart, already present in the embryonic life that persist into the



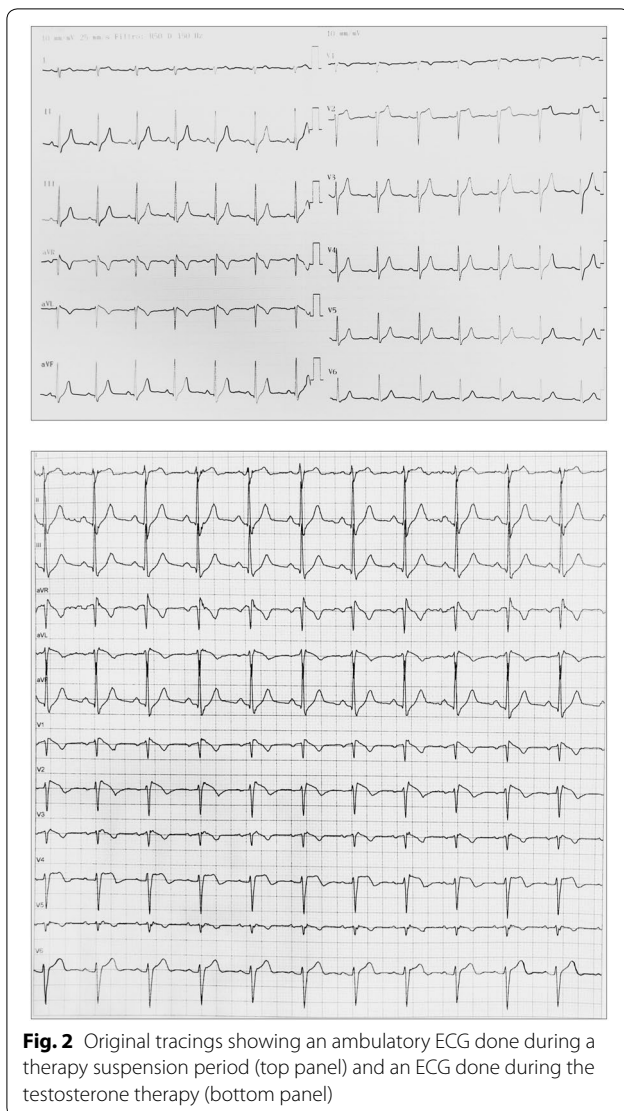


Fig. 2 Original tracings showing an ambulatory ECG done during a therapy suspension period (top panel) and an ECG done during the testosterone therapy (bottom panel)

adult life. One experimental study in dogs demonstrates that transmural difference in INa in female was reduced to values observed in male by testosterone [7]. If these results could suggest to hypothesise that INa dispersion is modulated by testosterone, this could be an important factor supporting gender differences in myocytes action potential duration dispersion and arrhythmias; similarly, we might assume that the same could happen on cardiomyocytes of a woman who is taking androgens.

Conclusion

A woman that undergoes a sex change is usually pre-treated with testosterone aiming at the virilisation of traits, including a deepening of the voice, the production of male-pattern body hair, growth and physical contours, and cessation of menses. In our case, as we have

clearly demonstrated by an appropriate test, the androgen administration/cessation was able to switch on and off a latent pattern of Brugada. Due to the general low prevalence of the Brugada syndrome our observation does not support to screen every female-to-male sex reassignment. On the contrary, it strongly supports a possible involvement of testosterone in ion channelopathies like the Brugada syndrome [8–10]. However, it will be prudent to offer a baseline ECG in preparation for the administration of testosterone in order to prevent the rise of a fatal syndrome.

Abbreviations

ECG: electrocardiogram; SCN5A: sodium channel, voltage-gated, type V, alpha subunit; IaN_a: late sodium current depolarising.

Authors' contributions

Each author contributed equally. All authors read and approved the final manuscript.

Availability of supporting data

Since it is a single case report, only clinical records were available.

Consent for publication

A consent form for anonymous publication of clinical data was obtained.

Competing interests

Not applicable.

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