High Prevalence of Prolonged QT Interval Duration in Male Patients with Cushing’s Disease

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Abstract ▼

Hypogonadal males have recently been shown to present prolonged QT interval, an electrocardiographic measure indicative of risk for fatal cardiac arrhythmias. Excess cortisol secretion induces low testosterone levels in male patients with Cushing’s disease but no study has yet evaluated if this is accompanied by changes in QT interval duration. We therefore decided to evaluate whether male patients with Cushing’s disease present changes in QT interval duration. QT interval was measured in electrocardiographic readings from 19 men and 35 women with Cushing’s disease and age- and sex-matched controls were used for comparison. QT interval was corrected for heart rate according to Bazett’s formula (QTc) and QTc > 440 msec and > 460 msec were taken as indicative of increased risk for torsade de pointes in men and women, respectively. Mean QTc was significantly longer in male patients compared with healthy controls (426.9 ± 9.27 vs. 389.7 ± 8.31, p < 0.05) and 5 men with Cushing’s disease presented prolonged QTc (prevalence 26%). By comparison, none of the women with Cushing’s disease presented prolonged QTc. Hypokalemia and low testosterone appeared associated with long QTc.

Conclusions: Male patients with Cushing’s disease present prolongation of QT interval which may lead to measurements associated with high risk for ventricular arrhythmias. Both low testosterone levels and hypokalemia appear to contribute to long QT in men with Cushing’s disease.

Introduction ▼

We have recently observed (Pecori Giraldi et al., 2010) that men with primary or secondary hypogonadism present high prevalence of prolonged QT interval, an electrocardiographic measure of ventricular repolarization duration and an important predictor for ventricular arrhythmias. Testosterone is believed to play a major role in QT interval duration in men (James et al., 2007); indeed, QT interval is comparable between sexes at birth and during childhood then shortens by some 20 msec in young males at puberty puberty (Stramba-Badiale et al., 1995; Pham and Rosen 2002; Rautaharju et al., 1992).

The shorter QT interval protects men from developing malignant ventricular arrhythmias such as torsade de pointes which, in fact, occur more frequently in women (Abi-Gerges et al., 2004). The gonadal axis is usually suppressed in patients with Cushing’s syndrome in both sexes and this contributes to several clinical features, e.g., osteoporosis, amenorrhea, reduced libido. No study has yet evaluated whether low testosterone levels impact cardiac repolarization in these patients; indeed, little is known of QT interval duration in Cushing’s syndrome, although several factors which affect QT duration, such as hypokalemia and ventricular hypertrophy (Oikarinen et al., 2001), often occur in patients with Cushing’s syndrome.

Given the above, we decided to evaluate the QT interval in patients with Cushing’s disease to ascertain whether this disorder is associated with an increased risk for ventricular arrhythmias.

Patients and Methods ▼

Study population

Our study comprised 19 men (age 37.2 ± 2.56 years, range 16–63 years) and 35 women (age 37.7 ± 1.74 years, range 16–62 years) with Cushing’s disease (Table 1). The diagnosis had been established by standard diagnostic procedures (Invitti et al., 1999) and confirmed by pathology and/or surgical outcome. 20 patients were hypertensives, 12 patients were overweight (BMI 25–30 mg/m²)
and 14 obese (BMI > 30 kg/m²). Medical history was negative for significant cardiologic events and no patient was on drugs with known risk for torsade de pointes (www.azcert.org). 54 age-and-sex-matched healthy subjects served as controls (Table 1). The study was approved by the Ethical Committee of our Institution.

Electrocardiogram
Standard electrocardiogram was performed and QT interval duration measured by a cardiologist blinded to the patients’ status and corrected for heart rate (QTc) according to Bazzett’s formula. The mean of 5 measurements for each lead was taken and the longest value considered (Schwartz et al., 1993). The upper normal limit for QTc was considered 440 msec in men and 460 msec in women (Schwartz et al., 1993). Electrocardiographic tracings were also reviewed for hypokalemia-induced prominent U waves. Left ventricular mass was established by gender-adjusted Cornell index and values greater than 2440 mm taken as indicative of left ventricular hypertrophy (Casale et al., 1987; Mancia et al., 2007).

Echocardiography (Hewlett Packard Sono 1500, Andover MA) was performed in selected patients, according to cardiologic recommendations, and left ventricular mass quantified as LMVi (left ventricular mass index; normal range < 50 g/m²).

Hormonal evaluation
Urinary free cortisol (DPC Coat-a-Count, Los Angeles, USA), serum cortisol and plasma ACTH were measured by commercial immunometric assays (Diasorin, Saluggia, Italy). Thyroid and gonadal hormones were assayed by electrochemiluminescence (ECLIA, Roche Diagnostics, Monza, Italy). Normal values in our laboratory for UFC, serum cortisol and plasma ACTH are 25-220 nmol/24h, 130-690 nmol/l and 10–50 pg/ml, respectively. Normal values for total testosterone, LH and FSH in adult males are 9.9–27.8 nmol/l, 1.7–8.6 U/l and 1.5–12.4 U/l, respectively. In women, normal ranges for estradiol, progesterone, LH and FSH in the follicular phase are 46–607 pmol/l, 0.6–4.7 nmol/l, 2.4–12.6 U/l and 3.5–12.5 U/l, respectively.

Statistical analysis
Wilcoxon’s test for paired data was used for comparison of continuous variables and chi-squared or Fisher’s exact test, as appropriate, for analysis of qualitative data. Linear regression analysis was used to establish associations with QTc measurements. Statistical significance was accepted for p < 0.05. Data are described as mean ± S.E.M.

Results
Men with Cushing’s disease presented significantly longer QTc intervals compared with age-matched controls (426.9 ± 9.27 vs. 389.7 ± 8.31 msec, p < 0.05) and, importantly, QT values fell into the abnormal range in 5 (26%, Fig. 1); this figure is considerably greater than the 2.5% proportion observed in the normal population (Schwartz et al., 1993). Conversely, QTc measurements yielded almost superimposable results in female patients with Cushing’s syndrome and their age-matched controls (398.0 ± 4.07 vs. 400.5 ± 3.18 msec, respectively, NS) and no woman with Cushing’s disease exhibited abnormal QTc interval duration.

At linear regression analysis, QTc measurements were inversely correlated with potassium levels (r = −0.448, p < 0.005) and hypokalemia was more frequent among patients with long QT interval (66 vs. 33%, p < 0.05). All men with Cushing’s disease presented secondary hypogonadism, i.e., total testosterone < 9.9 nmol/l and inappropriately normal LH/FSH concentrations, and QTc was negatively correlated with total testosterone levels.

Table 1 Demographical data of the study population.

<table>
<thead>
<tr>
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<th>Patients with Cushing’s disease</th>
<th>Healthy controls</th>
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<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>number</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>age (years)</td>
<td>37.2 ± 2.56</td>
<td>37.7 ± 1.74</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>26.7 ± 1.08</td>
<td>27.7 ± 1.46</td>
</tr>
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All comparisons N.S.

ECLIA, Roche Diagnostics, Monza, Italy. Normal values in our laboratory for UFC, serum cortisol and plasma ACTH are 25-220 nmol/24h, 130-690 nmol/l and 10–50 pg/ml, respectively. Normal values for total testosterone, LH and FSH in adult males are 9.9–27.8 nmol/l, 1.7–8.6 U/l and 1.5–12.4 U/l, respectively. In women, normal ranges for estradiol, progesterone, LH and FSH in the follicular phase are 46–607 pmol/l, 0.6–4.7 nmol/l, 2.4–12.6 U/l and 3.5–12.5 U/l, respectively.

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Diagnosis and management of Cushing's syndrome reported mostly non specific findings (Tsuda et al., 1995) and, while the original literature is not available, longstanding evidence suggests that Cushing's disease may cause ECG-detectable alterations (Ryzhikov 1978; Savel'ev and Stepanov 1962). QT interval, a measure of cardiac ventricular repolarization, has gained considerable interest as prolongation of this interval can predispose to fatal cardiac arrhythmias, most notably torsade de pointes. QT prolongation can be inherited (e.g., mutations in genes that modulate cardiac repolarization), drug-induced or secondary to cardiac disease, electrolyte derangements (e.g., hypokalemia) and other conditions (Al-Khatib et al., 2003; Roden 2004). Testosterone is an important modulator of QT interval length (James et al., 2007) and is believed to be causal to the shortening of QT interval in young males at puberty (Pham and Rosen 2002; Rautaharju et al., 1992). We have recently observed a high prevalence of prolonged QT interval in male hypogonadal patients (Pecori Giraldi et al., 2010) and believed it of interest to evaluate whether the QT interval is affected men with Cushing's disease, in whom testosterone levels are notably low. Our results indeed confirmed this suspicion as QTc interval was longer and the prevalence of prolonged QTc was considerably greater in male patients with Cushing's disease. It should be recalled that prolonged QT interval is estimated to occur in 2.5% individuals from the general population (Schwartz et al., 1993), far less than the 26% prevalence found in the present series of men with Cushing's disease. Conversely, all women with Cushing's disease presented normal QTc intervals thus linking our finding to gender-specific changes rather than hypercortisolism per se. Men with Cushing's disease are known to display a more severe clinical presentation and worse clinical outcome (Pecori Giraldi et al., 2003; Pecori Giraldi et al., 2007) although the underlying causes remain to be established. Suppression of the gonadal axis could be implicated in the greater prevalence of several such features, e.g., osteoporosis, postsurgical GH deficiency, and, as shown in the present study, prolonged QTc interval. A factor which was also closely related and probably contributed to prolonged QTc interval in the present series is hypokalemia, a known determinant of prolonged QT. Hypokalemia has also been linked to sudden death in a male patient with ectopic ACTH secretion in whom U waves and prolonged QT interval are reported (Scott and Friday 1988) and in the prolongation of QTc interval among patients with primary aldosteronism (Matsumura et al., 2005), a condition sharing several biochemical features with Cushing's syndrome. Obesity and hypothyroidism have also been associated with prolonged QT interval (Fraley et al., 2005; Fazio et al., 1992) but no association with BMI and thyroid function was detected in our series thus they are unlikely to play a role in the present finding. The present series is too small to draw significant conclusions on the course of this alteration after remission of hypercortisolism but data observed so far invite further studies.

In conclusion, our study highlights a possible, additional risk factor for acute cardiac events in male patients with Cushing's syndrome, namely QTc interval prolongation, which appears closely related to low levels of testosterone and hypokalemia and warrants further investigation. This finding enhances the more unfavourable clinical course of male patients compared with their female counterparts (Pecori Giraldi et al., 2003).

Conflict of Interest: None.

References
1 The University of Arizona center for Education and Research on Therapeutics. Drugs that prolong the QT interval and/or induce torsade de pointes ventricular arrhythmia (updated 8/9/2010). Available from: www.acertz.org/medical-pros/drug-lists/d1536.htm
3 Al-Khatib SM, LaPointe NM, Kramer JM et al. What clinicians should know about the QT interval. JAMA 2003; 289: 2120–2127
4 Casale PN, Devereux RB, Alonso DR et al. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. Circulation 1987; 75: 565–572
8 Lupoli E, Al-Khatib SM, LaPointe NM et al. What clinicians should know about the QT interval. JAMA 2003; 289: 2120–2127