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Hypogonadism as a reversible cause of Torsade de Pointes in men

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Long QT intervals corrected for rate (QTc), >480–500 msec, predispose to the polymorphic ventricular tachycardia Torsades de pointes (TdP).[1] Because QTc is shorter and TdP less frequent in men than in women, and testosterone shortens ventricular repolarization, we

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examined the effect of hypogonadism and androgen deprivation therapy (ADT) on QTc and TdP risk.[2]

We prospectively evaluated testosterone and related plasma levels in each male seen with TdP (n=7) over 19 months at a single university hospital (Hôpital Pitié-Salpétrière, Paris, France, Commission nationale de l'informatique et des libertés #1491960v0, patients informed consent obtained). We then analyzed the European pharmacovigilance database (up to 06/2017, Clinical Trial Registry Number #03193138) searching for QTc/TdP adverse drug reactions (ADR, Medical Dictionary for Regulatory Activities terms: Long-QT syndrome [LQT], electrocardiogram QT-prolonged and TdP) associated with ADT, and performed a cross-sectional analysis of association between international classification codes 9/10 for LQT/TdP and hypogonadism in 1.1 million men in a United States electronic health record (EHR) cohort (up to 11/2017, Vanderbilt University Medical Center, Institutional Review Board approval #171796).[3]

Hypogonadism was diagnosed in 7/7 cases of TdP (Table). After correction of low testosterone levels, QTc shortened and there was no TdP recurrence. Three patients had spontaneous reversal of hypogonadism after resolution of a severe critical illness, 3 needed testosterone supplementation for chronic hypogonadism, and one died. LQT genetic screening was negative in 6/6 tested patients.

The European pharmacovigilance database (http://www.adrreports.eu/fr/search.html) analysis identified 43/34221 individual case safety reports of men with drug-induced LQT (diLQT) and 15/34221 with diTdP suspected to be attributable to ADT vs none (0/10847) reported during testosterone replacement therapy. ADT included the following pharmacological classes of drugs: gonadotrophin-releasing hormone receptor agonists (leuprolide, buserelin, goserelin, triptorelin); gonadotrophin-releasing hormone receptor antagonist (degarelix); cytochrome-17 inhibitor (abiraterone); nonsteroidal androgen receptor antagonists (bicalutamide, flutamide, nilutamide, enzalutamide); 5α-reductase inhibitors (finasteride, dutasteride). Disproportionality analysis showed higher reporting odds-ratios (ROR)[4] comparing ADT vs. testosterone for diLQT and diTdP (ROR: 3.75–∞, $p<0.0001$; ROR: 1.3–∞, $p=0.03$; respectively). Degarelix and abiraterone carried the highest reporting rate for diLQT (n: 4/769, 0.52% for degarelix; n: 7/4723, 0.15% for abiraterone) and diTdP (n: 2/769, 0.26% for degarelix; n: 5/4723, 0.11% for abiraterone) as compared to other ADT (n: 32/28729, 0.11% for diLQT; n: 8/28729, 0.03% for diTdP, both $p<0.05$)

In the EHR cohort, conditions or drugs leading to hypogonadism were associated with LQT/TdP (86/38,041 cases vs. 649/1,082,891 controls; crude OR: 3.8 [3–4.7], age-adjusted OR: 4.8 [3.8–6.1]). Men with hypogonadism secondary to endocrine conditions carried the highest association with LQT/TdP as compared to ADT users and all other men [30/9202 (0.33%) vs. 56/28839 (0.19%) vs. 649/1,082,891 (0.06%), respectively, $p<0.0001$].

Taken together, these data provide consistent support for an association between hypogonadism in men and LQT/TdP. The association appears to be causal since correction of hypogonadism by testosterone-replacement therapy can treat and/or prevent TdP and ADT can lead to LQT/TdP. These results provide strong justification for a clinical

recommendation to investigate the possibility of hypogonadism when TdP occurs in men. Hypogonadism should be added to the list of risk factors for TdP and an increased awareness should prompt correction of other TdP risk factors in men receiving ADT.

Our findings support the hypothesis that hypogonadism is a correctable and readily identifiable risk factor for TdP in men. There should be a high index of suspicion when symptoms such as erectile dysfunction, testicular hypotrophy and hot flashes are present, particularly when the prevalence of hypogonadism is expected to be high such as in elderly men. It has been shown that hypothalamic-pituitary-gonadal axis physiology is dramatically altered during critical illnesses, following major surgery, or brain injury, and can lead to transient functional hypogonadism;[5] therefore, the distinction between transient hypogonadism in this setting and preexistent hypogonadism may be difficult. For these reasons, we postponed testosterone supplementation in patients #4 to #7 (sepsis, surgery or stroke; Table) awaiting a spontaneous normalization of pituitary function. Late-onset hypogonadism has recently been defined as a syndrome in middle-aged and elderly men reporting sexual symptoms associated with higher cardiovascular mortality in the presence of low testosterone-levels (e.g. patients #2 and #3).[5] In our case series, TdP did not recur after testosterone supplementation. The basic mechanisms are not completely defined but preclinical studies show that testosterone increases the repolarizing potassium currents I_{Kr} and I_{Ks} and decreases the depolarizing L-type calcium current.[2]

ADT is a cornerstone for treatment of prostate cancer. Among ADT, the website crediblemeds.org currents lists only degarelix and leuprolide as possible risks for TdP, so further guideline updates may be needed for other newer drugs, such as abiraterone.

A limitation of the analyses of the pharmacovigilance database and the EHR is that the data come from uncontrolled sources. Nevertheless, the case series and the population analyses provide orthogonal validation for the causal – and treatable – relationship we postulate between male hypogonadism and TdP risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table.1

Details of the seven cases of TdP identified with hypogonadism

Patient	Past medical history	Clinical presentation	Characterization of hypogonadism†*	Other liable drugs or conditions for TdP†	Outcome
#1, 72 yrs	- Hypertension, normal EF, ischemic cardiomyopathy on betablockers, Langerhans-cell histiocytosis infiltrating multiple organs with BRAF-mutation (ECD) since 2yrs treated by interferon-α - QTc~440ms before ECD; progressive prolongation after ECD: QTc~550ms concomitant to hypogonadism onset	- Respiratory distress and recurrent episodes of TdP, requiring six cardioversions for post-TdP ventricular fibrillation. - QTc>550ms, while on chronic beta-blocker	- No sexual activity with no erection for the past 6–8 months - Clinical examination: bilateral hypotrophic testes, gynecomastia. - Mixed central and peripheral hypogonadism, Bio-T: 0.5ng/ml, FSH: 9.5IU/l, LH: 11.6IU/l	- Plasma electrolytes and troponins normal. - Lung infection treated by spiramycin (but, after first episode of syncope)	- ICD implanted - Testosterone started for sustained hypogonadism related to his histiocytosis - QTc normalization within 4 days and no TdP recurrence at 1.5yrs despite vemurafenib introduction (ECD)
#2, 78 yrs	Paroxysmal atrial fibrillation on sotalol and digoxin, normal EF, progressive QTc prolongation over 4 yrs : QTc~460–480ms	- Syncopal TdP episodes 2 days after mitral valve replacement for endocarditis - QTc>600ms, paroxysmal atrio-ventricular blocks	- Progressive apparition of sexual symptoms over the past 5 yrs, probably due to late-onset hypogonadism - Mixed central and peripheral hypogonadism: Bio-T <0.1ng/ml, FSH: 16.6IU/l, LH:10.6IU/l	- Normal electrolytes and no acute ischemia - Bradycardia, paroxysmal atrio-ventricular blocks - Sotalol withdrawn before surgery. Time lag between withdrawal and TdP >5 days	- Temporary pacing - Persistence of QTc~500ms, 2 months after surgery - Testosterone administration at 3 months with normalization of sexual symptoms and QTc with no TdP recurrence at 1 yr
#3, 75 yrs	Pacemaker for paroxysmal bradycardia-tachycardia syndrome on amiodarone and bisoprolol (QTc~530ms), ischemic cardiomyopathy, EF: 35–45%, moderate renal failure	- Cardiac arrest on TdP 12h after elective pacemaker replacement - QTc: 660ms	- Chronic clinical signs of hypogonadism, probably due to late-onset hypogonadism - Peripheral hypogonadism: Bio-T <0.1ng/ml, FSH: 44.9IU/l, LH:51.3IU/l	- Normal electrolytes and no acute ischemia - Hydroxyzine before surgery, chronic amiodarone	- Persistence of QTc~550ms 1 week after amiodarone and hydroxyzine withdrawal - Testosterone administration 1 week post TdP with QTc shortening (~480ms) and no TdP recurrence at 3 months
#4, 90 yrs	Hypertension treated with diuretics, normal EF, borderline QTc (~460ms), cured prostate cancer, temporal arteritis on corticosteroids	- Syncopal TdP episodes requiring cardioversions in a context of paroxysmal atrial fibrillation and sepsis	- Mild chronic clinical signs of hypogonadism - Mixed central and peripheral hypogonadism; Bio-T:	- Severe hypokalemia (2mmol/l)	- Correction of hypokalemia, withdrawal of liable drugs - Spontaneous incomplete reversion of Bio-T: 0.7ng/ml, and shortening of

Patient	Past medical history	Clinical presentation	Characterization of hypogonadism†*	Other liable drugs or conditions for TdP†	Outcome
		- QTc>600ms	0.2ng/ml, FSH: 17.5IU/l, LH: 20IU/l	- Sepsis treated by ciprofloxacin and fluconazole	QTc (486ms) within 10 days - Testosterone not given (history of prostate cancer)
#5, 63 yrs	Hypertension, prostate adenoma, familial history of sudden death, normal QTc, normal EF, paroxysmal atrial fibrillation	- Multiple self-terminating TdP episodes in context of septic and hemorrhagic shocks - QTc: 508 ms	- No pre-existing signs of hypogonadism before shock - Central hypogonadism triggered by severe acute conditions; Bio-T <0.1ng/ml, FSH: 6.9IU/l, LH:10.7IU/l	- Shocks, extra-corporeal membrane oxygenation - Ventricular arrhythmias and ischemia on inotropes requiring amiodarone	- Spontaneous normalization of T-levels (Bio-T: 0.9ng/ml), and QTc (440ms) one month after recovery from shock
#6, 63 yrs	Hypertension, paroxysmal atrial fibrillation, systemic aneurysmal vasculopathy leading to multiple strokes complicated by epilepsy and hemiplegia, Normal EF, Normal QTc	- Cardiac arrest due to TdP leading to ventricular fibrillation (>15 cardioversions) - QTc~560ms	- No pre-existing signs of hypogonadism before TdP - Central hypogonadism triggered by acute severe conditions; Bio-T: 0.3ng/ml, FSH: 6.4IU/l, LH:4.4IU/l	- Normal electrolytes and no acute ischemia	Septic death 6 days after admission for cardiac arrest
#7, 72 yrs	Syncopal sinus node dysfunction with normal QTc requiring pacemaker, hypertension, normal EF, normal QTc	- TdP (QTc: 470ms) while hospitalized for transient cerebral ischemia - Recurrence of acquired prolonged QTc: 480ms, in context of endocarditis	- No pre-existing signs of hypogonadism before TdP - Central hypogonadism triggered by acute severe conditions; Bio-T< 0.1ng/ml, FSH: 0.5IU/l, LH:1.4IU/l (for endocarditis event)	- Normal electrolytes and no acute ischemia	- Spontaneous normalization of T-levels (Bio-T: 1.5ng/ml), and QTc (430ms) within weeks of acute events resolution - ICD upgrading while changing pacemaker

Abbreviations: Bio-T: bioavailable testosterone; ECD: Erdheim-Chester disease; EF: ejection fraction (left ventricle); FSH: Follicle stimulating hormone; ICD: implantable cardioverter defibrillator; LH: luteinizing hormone; ms: milliseconds; TdP: Torsade de Pointes, yrs: years

*Hypogonadic men with high FSH and LH were classified as having peripheral hypogonadism, whereas those with inappropriately normal or low FSH and LH were considered to have central hypogonadism. Normal values for adult men in our laboratory: FSH: 1.5–12.4 IU/l, LH: 1.7–8.6 IU/l, Bio-T: 1–3.2 ng/ml. A progressive decrease of Bio-T normal values are expected with increasing age (up to 40% at 90y).

†According to CredibleMeds website: https://crediblemeds.org/