Asociación Colombiana de Psiquiatría ACP

Revista Colombiana de Psiquiatría

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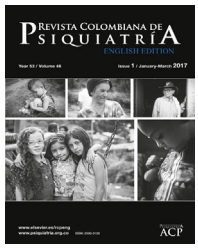

Case report

Adult Gender Dysphoria with Coronary Disease: Case Report and Literature Review☆

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ARTICLE INFO

Article history:
Received 16 August 2017
Accepted 16 October 2018
Available online 12 September 2020

Keywords:
Gender dysphoria
Transgender people
Drug therapy
Coronary disease

ABSTRACT

Introduction: Gender dysphoria (GD) refers to a marked incongruity between gender identity and biological sex. GD generates a significant clinical discomfort for at least six months.
Methods: Case report and non-systematic literature review.
Case presentation: A 56-year - old male-to-female patient, who had a history of coronary disease and a second thromboembolic event after hormone therapy (self-medicated). Once she had received acute management for the cardiovascular disease, she consulted for her GD.
Discussion: GD requires multidisciplinary management. Cross-sex hormonal therapy is considered the main treatment. It has been documented that oral oestrogen preparations may increase the risk of thromboembolic events in patients over the age of 40, especially when they have cardiovascular risk factors.
Conclusions: Comprehensive treatment should be offered to everyone who has GD, to relieve psychological distress, decrease psychiatric comorbidity and improve quality of life. To date, there is little scientific evidence regarding cross - sex hormonal therapy in transgender women over the age of 40; we therefore recommend multidisciplinary, close and rigorous monitoring, in particular when they have cardiovascular risk.

Disforia de género en el adulto con enfermedad coronaria. Reporte de caso y revisión de la literatura

Palabras clave:
Disforia de género
Personas transgénero
Tratamiento farmacológico
Enfermedad coronaria

RESUMEN

Introducción: La disforia de género (DG) hace referencia a una marcada incongruencia entre la identidad de género y el sexo biológico, que genera un malestar clínico de al menos 6 meses de duración.

DOI of original article: https://doi.org/10.1016/j.rcp.2018.10.003.
☆ Please cite this article as: Ocampo-Serna S, Gutiérrez-Segura JC, Vallejo-González S. Disforia de género en el adulto con enfermedad coronaria. Reporte de caso y revisión de la literatura. Rev Colomb Psiquiat. 2020;49:211–215.
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https://doi.org/10.1016/j.rcpeng.2018.10.008

Métodos: Reporte de caso y revisión no sistemática de la literatura.
Presentación del caso: Mujer transgénero de 56 años, con historia de enfermedad coronaria y un segundo evento tromboembólico posterior a la automedicación de terapia hormonal. Después del tratamiento agudo de su afección cardiovascular, solicitó tratamiento para su DG.
Discusión: La DG requiere un tratamiento multidisciplinario. La THC es el pilar del tratamiento. Se ha documentado que el uso de presentaciones orales de estrógenos puede aumentar el riesgo de eventos tromboembólicos en pacientes mayores de 40 años, principalmente cuando tienen factores de riesgo cardiovascular.
Conclusiones: Se debe ofrecer un tratamiento integral a todas las personas con DG para aliviar el malestar psicológico, disminuir la comorbilidad psiquiátrica y mejorar su calidad de vida. Hasta el momento hay poca evidencia científica respecto a la THC en mujeres transgénero mayores de 40 años, por lo que se recomienda una vigilancia multidisciplinaria, estrecha y rigurosa, en especial cuando hay riesgo cardiovascular.

Introduction

The classification of gender identity-related conditions has been changing. The term ẗranssexualismäppeared in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III), in 1980. The DSM-IV called it g̈ender identity disorder.̈ The current edition of the manual, the DSM-5, calls it gender dysphoria (GD).[1–3] GD refers to a marked incongruence between one's gender identity and biological sex resulting in significant clinical distress.[1]

Biological sex is genetically determined and tied to hormones and anatomy. Gender identity is defined as a feeling of belonging to a sex (female or male); usually it is expressed as gender role, which refers to the behaviours and attitudes attributed to a sex, based on social norms, historical period and culture.[3–5]

The World Professional Association for Transgender Health (WPATH) defines a transsexual person as a person who seeks to change or has changed his or her primary or secondary sex characteristics through feminisation or masculinisation interventions (hormones or surgery), accompanied by a permanent change in his or her gender role.[6] An individual whose biological sex is male and stated gender is female is called male-to-female transgender (MFT); an individual with female biology and a male gender identity is called female-to-male transgender (FMT).[6–8]

GD requires multidisciplinary treatment. People seek hormone therapy, with or without surgery, to change their physical appearance in order to align it with their stated gender and thus relieve the distress associated with living with an incongruent gender.[6,9]

As there is no consensus with regard to treatment for GD in adults with cross-sex hormone therapy (CHT) in the context of cardiovascular disease, it was decided to report a case and discuss the current scientific information.

Methods

Case report and non-systematic review of the literature.

Case report

A 56-year-old patient had a 46, XY karyotype and, since the age of four, a female gender identity. She was the youngest of five siblings. Her neurological development was as expected. When she was two years old, her biological mother died. During her childhood, she played games with both genders and socially played a male role. At age four, she started to dress in clothing for girls in secret, fearing the remarks her family might make. During puberty, she did not feel sexually attracted to either sex, although she established better relationships with female peers, because she felt that she d̈id not fit inẅith males her age. She developed male secondary sex characteristics in late adolescence. She began to have satisfactory sexual relations with women in adulthood, and with people of either sex after age 30. In her 20 s, she had a suicide attempt following a break-up with a partner. It was accompanied by self-limiting depressive symptoms for one week, during which she did not seek professional help.

At age 53, she suffered a first myocardial infarction, associated with symptoms of anxiety and insomnia. For one year, she was treated with sertraline 50 mg/day for a diagnosis made by psychiatry of generalised anxiety, but she did not come back for follow-up.

Following the acute coronary event, she started to publicly express her stated gender and began to self-medicate with oestradiol 1 mg and drospirenone 2 mg. Following five months, she had a second ischaemic event. Coronary disease was documented in three vessels and a cardiac resynchronisation therapy pacemaker was implanted due to heart failure

(ejection fraction 22%). She had a personal history of hypertension and occasional alcohol use and a family history of cardiovascular disease. Physical examination revealed normal vital signs and a body mass index of 23.1, as well as generalised decreased lung sounds, muffled normal heart sounds with no murmurs, and peripheral pulses with good intensity. Mental examination showed that she was dressed as a women, with suitable personal presentation, average intelligence, euthymia, logical and circumstantial thinking, and overrated ideas regarding gender change. Her language was fluent and prosodic, with a deep tone of voice. Her judgement was intact, her introspection positive and her prospection suitable. Paraclinical data: hormone study within normal limits for the patient's sex and age and all other laboratory results within normal limits, apart from slightly abnormal kidney function. A bone density scan reported osteoporosis in the femoral neck and the hips and vitamin D deficiency.

After six months of follow-up by endocrinology and psychiatry, it was decided to administer hormone therapy with oestradiol valerate 2 mg, once the patient had been informed of the risks and signed the informed consent form. The patient stated that she preferred "feeling like a woman" with hormone therapy, although it might have other physical complications. As the patient had difficulties with her health insurer and could not cover the cost, transdermal oestrogens could not be used. At first, oestradiol valerate was difficult to obtain, as it was considered a medicine "not for use in males", despite the fact that it was included in the patient's health benefits plan. Ultimately, as anti-androgen therapy she received spironolactone, which is indicated for heart failure, but her dose could not be increased due to mild hyperkalaemia. At present, she states that she feels more comfortable with herself, has experienced suitable social acceptance, and has not presented further affective or anxious symptoms. Regarding her gender identity, she said: "I feel like a woman in a man's body. I don't dress as a woman because I want to sleep with a man. For me, it's not about sexual attraction. It's about the fact that I've felt all my life that I am a woman."

Literature review

Gender identity is a multifactorial process that involves biological, environmental and cultural factors.[4,7] In genetic studies, there is greater gender incongruence in monozygotic versus dizygotic twins. However, the results of studies of polymorphisms in specific genes are inconsistent.[7,8]

In addition, sexual organ differentiation occurs before brain differentiation. The Y chromosome features the determining gene *SRY*, which promotes male gonad development, resulting in testosterone production and peripheral conversion of testosterone to dihydrotestosterone (DHT), which is involved in modifying the external genital organs between week 6 and week 12 of embryonic development. Meanwhile, sexual differentiation of the brain occurs in the second half of pregnancy; that is to say, the two processes are not synchronous. Based on this fact, it has been hypothesised that the effect or absence of testosterone in brain development may be linked to gender identity.[10] Prenatal and postnatal exposure to androgens could be involved in gender identity and development.[7]

The anatomical structures with the greatest sexual dimorphism (the anterior interstitial nucleus of the hypothalamus and the stria terminalis) have been reported to be similar to the stated gender of transgender individuals.[7,10] It is believed that sexual differences in brain morphology, connectivity and functioning underlie sexual differences in behaviour, psychopathology and cognitive performance. Males have a larger brain volume than females, whereas females have a greater cortical thickness. Following hormone treatment, there is a greater cortical thickness in FMT, possibly due to the effect of testosterone. A decrease in cortical thickness and expansion of the ventricles in MFT would be related to suppression of the effect of testosterone and oestradiol in the brains of individuals treated with hormone therapy.[8]

Environmental hypotheses are based on the parent–child relationship: it is postulated that the learning of parents' expectations and societal norms influences gender identity development. In addition, children show gender nonconforming behaviours after the age of three.[4]

People with GD have high psychiatric comorbidity[4,11,12] and usually have higher rates of depression, anxiety[12], self-harm and suicide[4,11]. This finding has been proposed as a response to the social stigma that these people face, as well as the discrimination, persecution, bullying and physical and sexual violence that they experience.[4,12] Transgender youth use more alcohol, tobacco and other psychoactive substances than their non-transgender peers.[4] Differential diagnosis is of fundamental importance, especially with transvestic disorder, which involves dressing in opposite-sex clothing as a sexual fantasy, without the individual considering himself or herself to belong to the opposite sex or wanting to start hormone therapy or undergo surgery; and body dysmorphic disorder, which involves concern about perceived defects or imperfections in one's physical appearance, which in some cases includes concern about one's breasts or genitals and a desire to have them removed. GD should also be distinguished from borderline personality disorder, due to a pattern of unstable self-image, which may include sexual orientation and/or gender identity; dissociative identity disorder, in which GD may appear in a dissociative identity; and psychotic episodes with delusions of belonging to a different gender.[5]

Ultimately, the psychiatrist will be responsible for making the diagnosis, treating mental comorbidities, exploring the possibility of preparing the patient to affirm his or her gender through medical interventions and engaging in ongoing patient follow-up.[6]

Discussion

The significance of this case lies in the difficulty and scientific controversies surrounding provision of CHT to adults with GD, specifically when it co-occurs with cardiovascular disease.

According to the seventh version of the WPATH guidelines, GD requires multidisciplinary treatment.[6] Treatment includes psychotherapy, CHT and gender reassignment surgery. CHT reduces the existing sex characteristics and develops the desired ones.[13] This treatment is believed to be essential,

as it may relieve psychological distress associated with GD, decrease mental comorbidity and improve quality of life in patients.[2,11,12]

CHT for MFT individuals seeks to shift the balance between oestrogens and androgens. Oestrogens and anti-androgens (spironolactone, cyproterone and gonadotropin-releasing hormone agonists) are used. Progesterone has been used to increase breast volume, but it is not highly recommended due to cardiovascular risk.[9]

Hormone therapy is not free from adverse effects. The use of oral oestrogens increases the risk of thromboembolic events in patients over 40 years of age. Spironolactone increases potassium levels and alters blood volume and blood pressure. This requires patients who receive this type of therapy to undergo medical follow-up; compliance in this situation is difficult due to costs, discrimination and socioeconomic and cultural barriers, among other reasons. Around 50% of people self-medicate before seeing a physician.[9]

Oestrogen therapy has been shown to increase triglycerides and high-density lipoprotein cholesterol and to decrease low-density lipoprotein cholesterol. In a meta-analysis of 23 studies, just 14 cases of acute myocardial infarction were reported in 1,073 MFT individuals. This figure is difficult to interpret in the absence of a control group. Another two studies have demonstrated an increase in cardiovascular mortality in MFT individuals compared to the general population. The relationship between cardiovascular risk and hormone therapy is complex, given that oestrogens' chemical nature, route of administration and dose and patients' state of cardiovascular health may yield variable results.[9]

MFT individuals have a high prevalence of myocardial infarction, compared to control women, but the prevalence is similar to that of males, which alludes to a risk consistent with biological sex, in this case male. Long-term CHT does not decrease the risk of coronary events in MFT individuals compared to non-transsexual males. These results might be explained by pre-existing differences between the two sexes.[14] The effects of oestrogen therapy in MFT individuals may depend on individual cardiovascular health when therapy is started, since it may aggravate prior cardiovascular disease in older MFT individuals, whereas it may have a beneficial cardiovascular effect on young, healthy MFT individuals.[9] The same occurs in post-menopausal women, as hormone therapy is protective if administered when little time has passed since cessation of menstruation, but becomes more deleterious as the lapse between the time of menopause and the start of hormone therapy lengthens.

Steroid sex hormones exert different direct and indirect effects on cardiovascular function due to their metabolic and vasoactive properties. Oestrogens have been postulated as mediators of the cardiovascular differences between the two sexes. Oestrogens promote vasodilation in females, but not in males; this is believed to be because women have greater expression of oestrogen receptors in their artery walls. Following menopause, the oestrogen receptors in the vascular beds decrease over time. That is why the effectiveness of hormone therapy is limited in women who went through menopause many years ago. It has been proposed that oestrogens are protective before the onset of severe atherosclerosis, but not when severe atherosclerosis is already present, as it has been found that oestrogens are pro-inflammatory and may facilitate instability of plaques and thrombosis. In addition, oral oestrogens increase production of angiotensinogen, which has an impact on blood pressure.[15]

Oestrogen administration in males is believed to be harmful based on the Coronary Drug Project, which demonstrated an increase in acute myocardial infarction and cardiovascular death. Not only should the action of oestrogens be taken into consideration, but also low testosterone levels have been demonstrated to be independently linked to higher cardiovascular mortality rates among men. This is significant because, in MFT patients, drugs and techniques such as orchiectomy leading to decreased androgens are used. However, the cardiovascular effects of testosterone are not as well-understood as those of oestrogens.[15] Among the limited studies that exist, most MFT individuals who had a myocardial infarction were at least 50 years old, had one or more cardiovascular risk factors (primarily tobacco use) and had been receiving CHT for a short period. Based on these results, it is recommended that older MFT individuals with known cardiovascular risk be closely monitored, especially when starting CHT. Future studies are needed on the possible mechanisms that contribute to increases in cardiovascular risk during CHT, as well as the safety of CHT in older MFT individuals.[9] There are no data on hormone therapy in people over 50 years of age, and it is difficult to extrapolate results in non-transsexual women due to the many differences that exist. Some clinics have proposed decreasing oestrogen doses as patients age.[16]

The risk of prostate cancer should also be considered in MFT individuals. It would be hoped that its incidence in these individuals is low due to chemical or surgical castration, but cases have been reported; hence, screening after the age of 50 is proposed.[16]

CHT has been shown to improve quality of life and depressive symptoms in people with GD. A systematic review and meta-analysis of 28 studies that enrolled more than 1,800 transgender people (around 1,100 MFT individuals) demonstrated that hormone administration improves quality of life and gender dysphoria in 80% (95% confidence interval: 72–88%), but suicide rates remain high even with hormone therapy.[9] Another systematic review concluded that there is little evidence of the beneficial effects of CHT on the mental health of people with GD, due to a lack of controlled trials.[11]

Therefore, it is necessary to provide suitable treatment to this population, given the risk of death of up to 51%, secondary primarily to suicide, psychoactive substance abuse, HIV infection and cardiovascular disease.[17]

Conclusions

Comprehensive treatment should be offered to all people with GD to relieve psychological distress, decrease psychiatric comorbidity and improve quality of life. To date, there is little scientific evidence with regard to CHT in MFT people over 40 years of age; therefore, close, rigorous surveillance of a multidisciplinary nature is recommended, especially in the presence of cardiovascular risk. More studies must be conducted in the future to determine the safety of CHT. In the meantime, the risks and benefits of CHT should be extensively

explained so that patients may make their own duly informed decisions.

Ethical considerations

For this case report, the patient's information was kept entirely anonymous, the confidentiality of the information was maintained and the patient signed the informed consent form.

Conflicts of interest

None.

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