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ATYPICAL PRESENTATIONS AND RESPONSES TO CROSS HORMONAL THERAPY IN TRANSGENDER PATIENTS.

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ABSTRACT:

AIM: To describe atypical presentations and follow-up of transgender men and women in situations of cross-hormonal therapy followed at a specialized outpatient clinic.

METHOD: a case series comprised of five transgender patients in which atypical findings at presentation and follow-up were observed.

RESULTS: Case #1: A 29-year-old transgender woman (TGW) presented with normal bone density and absence of fractures ten years after surgical castration induced by sexual affirming surgery. Possible mechanisms such as initial exposure to testosterone until the age of 19 by natural puberty followed by 9 years of high-dose oral estradiol may well be resulted in residual bone effect. Case #2: Diffuse scaling erythroderma in use of testosterone cypionate in transgenic man with uncertain pathophysiology. Case #3: False elevation of lean mass at full-body densitometry in a transgender woman, probably by inflammatory reaction and fibrosis between adjacent tissues and the surface of the silicone prosthesis in the hip and buttocks, facilitating the passage of Xrays and overestimating lean mass. Case #4: Evidence of gender incongruity during investigation for high stature in prepubertal male, rejecting the use of testosterone to close the epiphyseal cartilage and initiating the use of high doses of estrogen and antiandrogen. Case #5: Induced cross-puberty in a transgender boy 10 years of age due to severe gender dysphoria, preserving bone age and mental health. **CONCLUSION:** Our cases illustrate uncommon presentations and hormonal responses in transgender patients.

INTRODUCTION

Transgender is the term designated for a person who does not accept him or her biological sex and who behaves socially as someone of the opposite gender to his or her birth. A transgender man (TGM) is the individual who present the female biological sex, but wants to express the male gender. Transgender women (TGW) are those who present the male biological sex, but want to express the female gender. Such incongruity may have implications for social, psychological, affective, in addition to health. Personal rejection, social and suicidal ideation may be consequences of this gender dysphoria, as well as an increased risk of adverse effects when hormone therapy is used without medical supervision----.

In the United States, transgender people represented 0.3% of the population in 2011, corresponding to almost 9 million people. In the Netherlands, the prevalence was 0.8% for transgender men and 1.1% for transgender women''.

Hormonal therapy in transgender patients aims to induce opposite secondary sexual characteristics, and this is not free from risks or adverse effects as the doses used are at least temporarily higher than those used in hypogonadal men or women. After one year of optimized hormone therapy and in accordance to the minimum age of 18 years, the sexual affirming surgery can performed in those who want it.

Side effects of testosterone therapy for transgender men include systemic arterial hypertension, increased risk of coronary and cerebrovascular disease, liver abnormalities and increased hematocrit. For transgender women, venous thromboembolism, hepatic dysfunction.

The current recommendations for clinical practice are often not evidence-based, mostly from expert opinions.

Therefore, the atypical presentation and therapeutic follow-up of transgender patients submitted to cross-hormonal therapy is an novel topic with very few data reported in the literature.

METHODS

This is a series of cases, which was performed through the data base analysis from transgender patients attending our endocrine outpatient clinic. The study was approved by Institutional Ethics in Research Committee.

RESULTS AND DISCUSSION

CASE 1

NORMAL BONE DENSITY (BMD) AND ABSENCE OF FRACTURES IN TRANSGENDER WOMAN TEN YEARS AFTER SURGICAL CASTRATION FOR SEXUAL AFFIRMING SURGERY

A 38-year old TGW presented with gender dysphoria at the age of five and, after 19 years of age, started to use intramuscular estradiol enanthate 10mg plus algestone 150mg monthly. She underwent a mammoplasty with silicone implants at the age of 20, and genital surgery for gender affirmation at the age of 22. She continued with cross-hormonal therapy without medical follow-up until the age of 28. She was referred to our division at the age of 38 with no hormonal treatment for the last 10 years. LSBMD 1,112 g/cm^2, T-score -0.7 and Z-score -0.4, and FNBMD 0.912 g/cm^2, T-score -0.9 and Z-score 0.1, serum C-telopeptide was 0.222 ng/mL, spine radiography showed no morphometric fractures, serum 25OHD 31.2 ng/ml, serum albumin 4.3 g/dl, serum calcium 8.9 mg/dl, phosphorus 3.9 mg/dl, alkaline phosphatase 48 U/L, FSH above 150 mIU/ml, LH 30.19 mIU/ml, total testosterone 9 ng/dl, estradiol less than 10 pg/ml, and serum progesterone 0.2 ng/ml.

DISCUSSION

Sexual steroids have a pivotal role in the acquisition and preservation of bone mass----. Testosterone is more related to periosteal apposition, increasing cortical bone thickness, and estrogen to increased endosteal bone at cortical sites as well as trabecular bone. It is believed that testosterone contributes to bone health by being converted by aromatases into estrogens. It is also known that factors leading to hypogonadism as surgical castration generate a marked decrease in bone mass, which can lead to osteoporosis----. In the present case, the initial exposure to testosterone and the 9-year estradiol sequence at high doses may have led to a residual strengthening of the bone structure, as in the sequential treatment of osteoporosis, sufficient to maintain bone health after gonadectomy. In transgender patients, the risks of this therapy are completely unknown.

CASE 2

DIFFUSE SCALING ERYTHRODERMA DURING TESTOSTERONE CYPIONATE INJECTIONS IN A TRANSGENDER MAN

A 13-year old TGM, presented with gender incongruity from childhood, which worsened at the first signs of her isosexual puberty, leading to suicide ideation after menarche. Cross puberty was induced by using testosterone cypionate 100mg per week, but after six months of use, he developed severe diffuse scaling erythroderma. The intramuscular (IM) use of this testosterone ester was stopped and self-administration of gel via transdermal was initiated.

DISCUSSION

Intramuscularly testosterone is the first line approach to TGM being most effective in promoting masculinization. Alternative routes can be chosen during the maintenance period as subcutaneous (SC), oral or transdermal. However, in this case, the patient presented diffuse scaling erythema in the use of testosterone injections, a fact not yet reported in the literature. It is known that transdermal testosterone systems may cause local erythema. In the present case the cutaneous reaction presented during testosterone injections may well be due to petroleum-derived products such as vaseline contained in these formulations increasing the antigenicity of testosterone to dendritic cells and Th2 cells in the skin. The use of testosterone SC, although effective, safe, economical, with few side effects and easy administration, can also cause some cutaneous reactions such as small, self-limited local nodules and small urticarial areas . One reported case related to the development of diffuse pruritic scaling erythema in an elderly hypogonadal man following the application of 900 mg-testosterone pellets. This condition ceased after the use of topical clobetasol for one week, and relapsed after a new SC testosterone cycle even at a lower dose.

CASE 3

FALSE ELEVATION OF LEAN MASS AT WHOLE BODY DENSITOMETRY IN TRANSGENDER WOMEN

A 24-year old TGW presented gender dysphoria since the age of 5 years. At age 14, she underwent the application of industrial silicone on hips and buttocks, obtaining satisfactory female proportions. At age 16, she started on injectable estrogen plus progesterone without medical supervision. She had gender-affirming surgery at age 19 and currently has irregular use of estrogen. BMD showed a Z-score of -2,3 in the femoral neck and -2,3 in the lumbar spine. Whole body DXA showed a total lean mass of 26.271kg, in addition to intense artifact effect at buttocks, thights and legs (Figure 1), corresponding to 22.120kg of lean mass. Using multifrequence electric bioimpedance (BIA), total lean mass was 23.1kg, a difference of 13.7% less than the total what was observed with DXA. Magnetic resonance imaging of buttocks and thighs showed diffuse obliteration of the subcutaneous tissue, without underlying skeletal muscle alterations, secondary to previous injection of a chemical substance for aesthetic purposes (Figure 2).

DISCUSSION

Interferences with body composition analysis by DXA caused by silicone implants were reported in only one case in the literature, where it does not show alterations in relation to lean mass and adipose tissue. Only changes in bone parameters such as a 17.9% increase in bone mineral content in the trunk containing silicone breast implants were demonstrated. In this case, there is a significant increase of lean mass in lower limbs when comparing this same parameter with multifrequency electro-bioimpedance evaluation, which shows a reading of the silicone as a muscular structure in the radiological analysis. There is no report in literature of the effect of silicone on lean mass. One of the possible explanation for the muscle mass overestimation may be related to the inflammatory reaction and consequent fibrosis between adjacent tissues and the silicone surface, facilitating the passage of X-rays and causing an overestimate of lean mass.

CASE 4

EVIDENCE OF GENDER INCONGRUENCE DURING HIGH STATURE RESEARCH

A 15-year old TGW, presented for evaluation of tall stature. He was 182 cm tall and was very unsatisfied with his height. The target height, for mid parental height, was 179.5 cm and his arm-span was 188 cm, testicular volume was 6 cc, BMI was 18.2 kg/m2 and bone age was 14 years (with an estimated final height of 196.3 cm). He also referred an intense gender dysphoria which led him to become isolated from school and society with symptoms of major depression. He had been on psychiatric care for 2 years. It was then decided with his parents to start on oral estradiol 4 mg plus spironolactone 100 mg per day. This resulted in complete feminization during the following year along with marked improvement in depression. After 2 years of estrogen therapy growth plates fused and the final height was 191 cm.

DISCUSSION

This case illustrates that in the face of severe dysphoria during adolescence, high doses of estrogen and antiandrogen were used to induce cross puberty, limit the unwanted tall stature effects and improve the patient's mental health. This emphasizes that the arbitrary age of 16 for initiation of cross-hormone therapy may not be justified in selected cases.

CASE 5

INDUCED CROSS PUBERTY IN TRANSGENDER BOY AT 10 YEARS OF AGE DUE TO SERIOUS GENDER DYSPHORIA

A 10-year old TGM presented with severe gender dysphoria at 3 years of age, when he hardly preferred male attitudes. She presented with early childhood depression and social isolation during the school phase. At age 7, he wrote a suicide letter. He moved to another city and adopted a masculine trait and behavior which were well received by her mates, without generating suspicions. When thelarche started, she felt bad again and was then referred to our endocrine division. Intramuscular testosterone cypionate was started at the dose of 100 mg each month. She

progressively developed a male pattern of hair growth with cessation of breast development and clitoris enlargement. Growth velocity went up to 10 cm/year and without advancing bone age.

DISCUSSION

This is another example that the arbitrary age of 16 to recommend the initiation of cross-hormone in adolescent transgender patients may be not adequate. In the present case there was an early-childhood severe dysphoria which showed an initial improvement by a radical social attitude. This may not be feasible for the majority of children. The return of depression and anxiety with the first pubertal signs makes the cases unique. Another important point of this case was the non-use of GnRH analogues for pubertal arrest. With small doses of testosterone used the patient had a good progression in terms of heterosexual pubertal development as well as growth. Although few studies reported cross-hormone therapy in children under 14 years of age, this case represents a good example of how to achieve mental health and growth improvements leading to better body and social transition in children [1,2].

Our cases illustrate unusual presentations and hormonal responses in transgender patients. The study of atypical clinical presentation and follow-up in transgender patients in situations of cross-hormonal therapy is a new and fascinated area in the field of endocrinology with so much to be scientifically explored.

DISCLOSURE

The authors haven't relationships with companies that may have a financial interest in the information contained in the manuscript. All the authors have contributed significantly for this publication and they are in agreement with the content of the manuscript.

FIGURES'S SUBTITLES

FIGURE 1: Whole body DXA showing intense artifact effect at buttocks, thights and legs, increasing the lean mass.

FIGURE 2: Magnetic resonance imaging (MRI) of buttocks and thighs showing diffuse obliteration of the subcutaneous tissue, without underlying skeletal muscle alterations. A: T1-weigth MRI; B: T2-weight MRI.

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