2017 AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/ENDOCRINE SOCIETY UPDATE ON TRANSGENDER MEDICINE: CASE DISCUSSIONS

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ABSTRACT

Objective: Increased numbers of transgender and gender-nonconforming people are presenting to physicians in the United States and abroad due to increased public recognition and acceptance and increased access to healthcare facilities. However, there are still gaps in medical knowledge among endocrinologists and other health care professionals. The purpose of these cases is to present several common clinical vignettes of transgender people presenting in an office setting that illustrate some of the key recommendations of the Endocrine Society's revised Endocrine Treatment of Gender Dysphoria/Gender Incongruent Persons guidelines, cosponsored by the American Association of Clinical Endocrinologists.

Methods: Cases were developed based on these recently revised guidelines for gender-dysphoric and gender-nonconforming persons.

Results: Six cases are presented that illustrate the diagnosis, treatment, and long-term management of transgender children and adults based on the revised guidelines for the endocrine care of gender-dysphoric and gender-nonconforming persons. Several key teaching points are presented from the presentation of these cases.

Conclusion: Endocrinologists should be familiar with the revised guidelines for gender-dysphoric and gender-nonconforming persons. Important aspects of care are the diagnosis of gender dysphoria, the timing of treatment with gender-affirming hormones, and the long-term monitoring for potential adverse outcomes. Long-term health outcome studies are needed to further help guide care in this unique population. **(Endocr Pract. 2017;23:1430-1436)**

Abbreviations:
BMI = body mass index; **GnRH** = gonadotropin-releasing hormone; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein

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CASE 1

Initiating and Monitoring Hormone Therapy in a Transgender Woman-Part I

A 50-year-old transgender woman is referred to you for hormone therapy initiation. The psychiatrist's referral letter states that the patient was assigned male at birth but has experienced a persistent desire to be female since age 5. She recalls playing with dolls and dressing in feminine clothing as a child, but she was not allowed to express herself as a female in public. She experienced adolescent bullying and did not quite fit in with her peers. She suppressed her desire to be female, married a woman, and had two children. Recently, she has experienced depression and started seeing a psychiatrist, who confirms that she meets the Diagnostic and Statistical Manual of Mental

Disorders (DSM)-V criteria for gender dysphoria and that she is ready to start hormones. What is the next step for the endocrinologist?

Discussion

This case highlights the issue of diagnosing persistent gender dysphoria in adulthood and appropriate initiation of hormone therapy. The guidelines recommend that the clinician confirm the diagnosis prior to initiating hormone therapy in transgender adults (Recommendation 3.1) (1). Clinicians with expertise in diagnosing adult gender dysphoria may make the diagnosis (Recommendation 1.1) (1), whereas those lacking the experience should provide a referral for diagnosis. Gender dysphoria should not be considered a mental disorder, and specialized mental health training is not required. However, sufficient knowledge is necessary to differentiate gender dysphoria from other problems such as body dysmorphic syndrome and to recognize psychopathology that may interfere with satisfactory treatment outcomes. Patients with gender dysphoria should fully understand the risks and benefits for the treatments and be able to provide informed consent (Guidelines Table 4). The guidelines also recommend that clinicians prescribe therapies that bring the sex steroid levels into the range of the affirmed gender and evaluate the patient for conditions that can be exacerbated by hormone therapy (Recommendations 3.2, 3.3) (1).

In this patient, a psychiatrist has already confirmed the diagnosis of gender dysphoria. After a careful history and physical exam for conditions that can be exacerbated by estrogen, such as thromboembolic disease, hormone-sensitive cancers, cardiovascular disease, and cholelithiasis (Guidelines Table 10), hormone therapy may be initiated using a combination of estrogen and a testosterone-lowering agent (Guidelines Table 11) (1). The risks of hormone therapy and the time course of expected changes should be discussed (Guidelines Table 12 and 13) (1). Given the risk of infertility associated with hormone therapy, the patient may consider sperm cryopreservation. Estrogen is available as a pill, patch, or cream, and as intramuscular injections (Guidelines Table 11) (1). Some data suggest that oral estradiol is safer than conjugated estrogens in transwomen. Estradiol levels cannot be measured in patients taking conjugated estrogens, making monitoring of estrogen levels impossible. One retrospective study found that transwomen taking conjugated estrogens had an increased risk of thromboembolism compared to those taking oral estradiol valerate (2). Some data suggest that estrogen patches may cause fewer adverse reactions compared to pills, although head-to-head studies have not been published (3). Testosterone may be lowered using spironolactone, cyproterone acetate, or a gonadotropin-releasing hormone (GnRH) agonist. Due to lower costs, most transwomen are prescribed spironolactone (100 to 300 mg daily) (Guideline Table 11) (1).

Initiating and Monitoring Hormone Therapy in a Transgender Woman-Part II

The physician discusses all the potential formulations of estrogen treatment, including estradiol pills, patches/gels, or injections. Further, the physician suggests that estradiol patches may have less risk of complications than oral estrogens due to less stimulation of blood coagulation factors. Furthermore, the risks of oral estrogen may be higher in an older patient than a younger patient. However, the patient prefers the convenience of an oral estrogen and is started on oral estradiol 2 mg daily and spironolactone 50 mg twice daily and returns to see you in 3 months. She describes feeling less anxious and depressed, having to shave less, and having fewer erections. She also describes some breast changes with nipple tenderness. However, she is still not completely satisfied and wants to try another form of estrogen. What should be done to her hormone regimen?

Her Laboratory Tests Were as Follows:
Before Hormone Therapy
Estradiol: 20 pg/mL
Testosterone: 546 ng/dL
Prolactin: 12 ng/mL
Normal serum electrolytes

After Hormone Therapy
Estradiol: 96 pg/mL
Testosterone: 120 ng/dL
Normal serum electrolytes

Discussion

This case highlights the importance of hormone therapy monitoring and discussion of the expected time course for physical changes (Guidelines Table 13) (1). Estradiol and testosterone levels should be kept in the physiologic range expected for a female (estradiol concentrations 100 to 200 pg/mL and testosterone concentrations <50 ng/dL) (Guideline Table 15) (1). Clinicians should evaluate the response to hormone therapy by evaluating sex steroid hormone concentrations and querying for any potential adverse events every 3 months during the first year and 1 to 2 times a year thereafter (Recommendation 4.1) (1). In this patient, estradiol is low and testosterone is high for a premenopausal female. Changing to a different estrogen formulation is not necessary. The estrogen dose can be increased, and a transdermal formulation may be considered to lower the risk of long-term complications, which may include thromboembolism, given the patient's age. Since the patient's testosterone level remains above the physiologic range for a female, the spironolactone dose should also be increased. The guidelines do not support adding finasteride, which will not lower testosterone values and can be associated with increased mood disturbances (4).

CASE 2

Evaluation of a Transgender Child

A child, assigned male at birth, first visited the gender clinic at age 9 years for gender dysphoria. She liked to wear dresses and make-up but did so only at home because of feelings of shame. She mainly played with girls and recently announced that she was a girl. Upon physical examination, she was prepubertal. She was diagnosed with gender dysphoria by the gender team psychologist and child psychiatrist. The patient started puberty at 11 years of age (Tanner stage was G2; testicular volume of 5 mL). She found the prospect of puberty distressing and wished to start suppression treatment. Although her parents were supportive, she did not yet present herself as a girl in public. The psychologist concluded that the gender dysphoria had persisted, no psychosocial problems were present that might interfere with treatment, and she was capable of giving informed consent.

Should this transgender girl have received endocrine treatment when she first presented at age 9 years? Is treatment indicated now at the start of puberty? What is the best treatment option, and which side effects need to be discussed? What monitoring is necessary during treatment?

Discussion

Although gender dysphoria may manifest at an early age, studies have shown that it may not persist into adolescence and adulthood in the majority of children (5-7). A diagnostic evaluation at a gender clinic may help families understand the child's feelings and behavior. The gender team can also help the family find the best ways to support the child with gender dysphoric feelings. The guidelines recommend against medical interventions such as puberty blocking or gender-affirming hormone treatment in prepubertal children (Recommendation 1.4) (1). Gender dysphoria should be re-assessed once children enter puberty. Worsening (or emergence) of gender dysphoria at the onset of puberty must be present to consider puberty suppression (Guidelines Table 5). In addition, the child should have sufficient mental capacity to give informed consent. Only a qualified mental health professional with training and experience in child and adolescent developmental psychology should make such assessments (Recommendation 1.2) (1). In addition, the guidelines recommend an experienced professional assist the child and family with decisions regarding social transitioning (Recommendation 1.3) (1). In adolescents who have not reached the legal age of majority, informed consent of parents/guardians is also required for treatment (Guidelines Table 5) (1).

For adolescents with persistent gender dysphoria who have started puberty and request treatment, pubertal suppression using GnRH analogues, which is reversible and highly effective, is recommended (Recommendations 2.1 to 2.3, Guidelines Table 5) (1). The effects and side effects of GnRH analogue treatment, including effects on bone health and fertility, should be discussed.

GnRH analogue suppression of puberty is associated with (reversible) suppression of spermatogenesis. If adolescents subsequently start estradiol treatment, their fertility may be impacted, although precise studies regarding the effect of estrogens upon spermatogenesis in later puberty are not available, and orchidectomy will result in irreversible infertility. Before treatment is started, options to preserve fertility should be discussed at each phase of treatment (pubertal suppression, estrogen treatment, or surgery) (Recommendation 1.5) (1). Cryopreservation of sperm is commonly used to preserve fertility, but this may not be possible in early pubertal adolescents.

Once treatment has been started, the efficacy of pubertal suppression, treatment satisfaction, and any side effects should be assessed during regular follow-up visits (Guidelines Table 7) (1). Side effects, such as hot flushes, are common in adults and older adolescents but not in early pubertal adolescents. Effects on growth and bone health are a concern. Careful monitoring of growth, pubertal development, bone maturation, and bone mineral density is recommended (Guidelines Table 7) (1). Sufficient physical activity and calcium/vitamin D intake are advised.

CASE 3

Evaluation of Gender Dysphoria and Initiation of Hormone Therapy in a Transgender Adolescent

An adolescent, assigned female at birth, preferred stereotypical societal masculine behaviors as a child and realized he was a transgender boy at age 14 years. After a diagnostic evaluation confirmed that he had persistent gender dysphoria, he started GnRH analogue treatment to suppress puberty at age 15 years. At the time, his breast development was at Tanner stage 3, and menarche had not yet occurred. Endocrine evaluation prior to the start of GnRH treatment was unremarkable, and he had a withdrawal bleed after receiving GnRH treatment. The GnRH treatment was well-tolerated and improved his mood. During the treatment, he was seen at regular intervals by a gender team psychologist and pediatric endocrinologist. At age 16 years, his gender dysphoria persisted, and he wished to start testosterone treatment. He specifically looked forward to a more masculine voice. His family was supportive.

Which issues need to be addressed before testosterone treatment is started? Which investigations are necessary? What medication do you prescribe and at what dose?

Discussion

Before initiating testosterone therapy, a mental health professional should confirm that the gender dysphoria is persistent, no psychological or social problems are present

that could interfere with treatment, and the adolescent is mentally capable of giving informed consent (Guidelines Table 5). The adolescent should be informed of the reversible and irreversible (e.g., voice-lowering) effects of testosterone. In addition, the patient should be aware that androgens interfere with ovarian function and fertility, and options for fertility preservation should be discussed, such as cryopreservation of oocytes retrieved after ovarian stimulation. Even when these issues have been discussed prior to GnRH analogue treatment, they should be discussed again before testosterone treatment is initiated. In addition, the adolescent also needs to be advised about contraception if he has vaginal intercourse, as testosterone therapy is not an effective form of contraception, nor does it protect against sexually transmitted diseases. A complete medical history and physical examination are necessary to assess any contra-indications for testosterone treatment, such as erythrocytosis or severe liver dysfunction (Guidelines Table 10), even though such conditions are rare in adolescents. Several laboratory parameters should be monitored at the start of and during treatment, including hematocrit and lipid levels, bone age, and bone mineral density (Guidelines Table 9). In this case, the low-density lipoprotein (LDL) cholesterol level was elevated at baseline. Studies have shown that testosterone therapy in transgender persons may adversely affect the lipid profile (8); however, this is not a contra-indication for testosterone treatment. In this case, the adolescent was advised to engage in regular exercise, maintain a healthy weight, and refrain from smoking.

Testosterone can be given as injections or transdermally (Guidelines Table 11). Intramuscular testosterone esters are commonly used for pubertal induction and are generally preferred in early pubertal adolescents. These can be administered by the family physician/nurse or by the adolescent after appropriate instruction. At the end of pubertal induction, adolescents may change to transdermal testosterone therapy, although many adolescents find daily administration of gel bothersome. In adolescents who have not yet completed endogenous puberty, testosterone is started at a relatively low dose (25 mg/m^2 every 2 weeks) and increased gradually to an adult dose over the course of 2 years to mimic normal pubertal development and to optimize growth (Recommendation 2.4, Guidelines Table 8) (1).

In adolescents who have undergone endogenous puberty and reached adult height, testosterone may be started at a higher dose (75 mg every 2 weeks) and increased more rapidly (Guidelines Table 8). Effects and side effects of treatment, along with patient satisfaction, should be monitored during regular follow-up visits (Recommendation 2.6) (1). This patient may also eventually request breast surgery. The guidelines recommend the timing for breast surgery for transgender males to depend on the physical and health status of the individual (Recommendation 5.6).

CASE 4

Evaluation of a Transgender Adult for Gender-Affirming Surgeries

A 21-year-old Caucasian college graduate assigned male gender at birth presents to your office with the desire to transition to the female gender. The patient is asking about removal of male genitalia and vagina formation. The patient is also concerned about her prominent "Adam's apple" (larynx). She wore gender-neutral clothing and had a somewhat masculine haircut. Upon routine questioning, she stated that she was a pharmaceutical sales representative covering a large metropolitan territory. She plans to continue in the same job after transition. She has not yet spoken to her human resources department but is confident that she can continue in her current job as a female. She usually presents as male at work and as female at home and occasionally when going out at night. Her friends and family are supportive of her desire to change. She recently began low-dose estrogen therapy (2 months) and is now inquiring about genital and larynx surgery. The surgeon has some reservations and consults you as the treating endocrinologist.

Discussion

This case highlights the importance of a well-supported diagnosis and prior hormone treatment before initiation of gender-affirming surgery in adults. The guidelines emphasize that genital gender-confirming surgery is often necessary for the patient to live successfully in the affirmed gender and to relieve gender dysphoria. Of the various transfeminine genital surgeries, removal of the gonads and penis is the most regulated. With modern surgical techniques and an expert surgeon, the genitalia can be made to be almost identical with those of the affirmed gender. For operations required to make the penis into a vagina, it is particularly important to preserve the neurovascular bundle so that the newly formed clitoris will retain enough sensitivity to facilitate climax. The patient needs to understand the expected results, possible complications, and the cost/length of hospitalization. The patient should also understand that the surgical rehabilitation plan, which includes regular neovaginal dilations, can be time consuming and uncomfortable.

Prior to the request for surgery, the patient had undergone <2 months of hormone therapy and dressed in gender-neutral clothing. Current Endocrine Society Guidelines recommend that prior to genital surgery, patients must have made considerable progress in dealing with work, family and interpersonal issues, complete 1 year of gender-affrming hormones, unless contraindicated or not desired, and live full time in the new gender role prior to receiving gender-affrming genital surgery (Recommendations 5.2 and 5.4, Guidelines Table 16).

For some patients, the most important gender-affirming surgeries are chest-conforming surgery, breast augmentation, or tracheal shaving. These surgeries do not affect sexual functioning or fertility and thus have less-stringent criteria for approval. Living in the affirmed gender role and/or hormone therapy are not required prior to these surgeries. When considering breast augmentation, the patient and physician should note that breast size will continue to increase for 2 years after initiation of estrogen therapy. For this patient, referral to a speech language pathologist for voice therapy may enhance her female gender. Simultaneously, the patient should begin a year-long program of estrogen therapy, during which she would explore whether gender-affirming surgery is appropriate with her gender expression (Recommendations 5.2 and 5.4 and Guidelines Table 16).

CASE 5

Monitoring Hormone Therapy in a Transgender Man-Part I

A 34-year-old transgender man reports great satisfaction after 10 years of testosterone therapy. He has lived successfully as a man since his teenage years. He recently moved and needs a new physician to prescribe his current hormone regimen, testosterone enanthate 120 mg subcutaneously every week. The patient had chest reconstruction surgery at age 18 but has not had other surgeries. He reports near-perfect compliance with his testosterone injections and has not had a menstrual period since starting therapy. He is virilized appropriately. His only concern is significant acne. Laboratory testing reveals a hematocrit of 55%. What adjustments, if any, should be made to his hormone regimen?

Discussion

While not all transgender individuals seek medical intervention, the majority of patients seen by an endocrinologist are likely to be seeking hormonal treatment. For transgender men (female to male), hormone treatment typically consists of testosterone to bring the serum testosterone from the female to the male range. Similar to intramuscular administration, stable testosterone levels can be achieved with subcutaneous injection of testosterone at the usual doses (50 to 100 mg per week) (10). Testosterone therapy is safe, but the case highlights a well-established concern: androgen-stimulated erythrocytosis. Hematocrit should be measured every 3 months for the first year and then one to two times a year (Recommendation 4.1, Guidelines Table 14) (1). Hematocrit levels above 54% may require a dose reduction, especially for patients with symptoms of erythrocytosis. Reducing the dose of testosterone may also improve the acne.

Potential causes of erythrocytosis, including tobacco use and sleep apnea, should be addressed (11). Sleep apnea may be exacerbated over time due to increased midline structure growth under the influence of male androgens. Although androgen therapy is likely to raise the hematocrit, the increase is usually within the normal range. However, androgen therapy can unmask polycythemia and may exacerbate concern in patients with borderline high hematocrit levels (12). Thus, monitoring of hematocrit is essential in transgender males. Measurement of peak and trough levels of free and total testosterone, as well as sex hormone–binding globulin levels may clarify the reason for this patient's erythrocytosis and acne (13).

Monitoring Hormone Therapy in a Transgender Man-Part II

Laboratory testing revealed a peak testosterone level of 850 ng/dL 24 hours after an injection (before injection, 410 ng/dL). The patient had a normal body mass index (BMI), no sleep apnea, and no history of smoking. What are the next best steps in the management of this patient?

Discussion

Without a secondary explanation, the elevated hematocrit could be addressed with lower testosterone doses as long as levels appropriate for bone health and cessation of menses are maintained. Studies showing less erythropoiesis with transdermal testosterone have been reported, but the consistency of these data remains unclear (14). Although the dose of testosterone is somewhat high, the actual laboratory data show only modest testosterone levels. When the testosterone regimen is modest but the hematocrit levels are high, hematologic evaluation may be considered to exclude the possibility of an underlying primary polycythemia. Treatment with phlebotomy may also be considered if reduction of the testosterone dose does not lower the hematocrit and after work-up for potential causes.

CASE 6

Initiation of Hormone Therapy in a Transgender Boy

A sedentary 17 year-old transgender male presents to the clinic to discuss hormone therapy for gender dysphoria. For several years, he has been treated by a psychologist and a psychiatrist for anxiety disorder and gender dysphoria. He came out in high school to his family, friends, and classmates, who have all been supportive. A letter from his therapist indicated that he would be a good candidate for hormone therapy with testosterone. On physical examination, his vitals included a height of 5 feet 6 inches, a weight of 176 pounds (80 kg), and a BMI of 28 kg/m^2. Baseline laboratory tests were notable for a total cholesterol of 246 mg/dL (desirable, <200 mg/dL), a triglyceride level of 195 mg/dL (desirable, <150 mg/dL), a high-density lipoprotein (HDL) cholesterol level of 40 mg/dL (desirable, ≥60 mg/

dL), and a LDL cholesterol level of 167 mg/dL (desirable, <100 mg/dL).

Should testosterone therapy be initiated at this point? Should the patient's overweight status and dyslipidemia be addressed?

Discussion

Testosterone therapy in transgender men has been associated with changes to both body composition and lipids. During the first 1 to 2 years of testosterone therapy, body weight and BMI generally increase by 4.8 to 7.7 pounds and 0.8 to 2.0 kg/m^2, respectively. Most studies found that body composition changes involve a decrease in fat mass and an increase in lean mass. Testosterone therapy (1 to 2 years) in transgender men typically lowers HDL cholesterol by 4 to 13 mg/dL and raises triglycerides by 6 to 32 mg/dL (15). Some studies have also demonstrated an increase in total cholesterol. One case-control study reported an increased incidence of type 2 diabetes in transgender men treated with testosterone (16). The guidelines recommend screening for cardiovascular risk factors, including measurement of fasting lipid profile (Recommendation 4.3) (1).

This patient was started on a low dose of intramuscular testosterone cypionate (50 mg/2 weeks) to determine his response. He was also advised to begin an exercise program and meet with a nutritionist to improve his fitness, weight, and overall health. At his 3-month follow-up visit, he had not met with a nutritionist nor begun an exercise program. His body weight had increased to 194 pounds (BMI, 31 kg/m^2).

Over the following 15 months, his testosterone dose was increased to 100 mg every 2 weeks. He did eventually meet with a nutritionist but struggled to make healthy food choices or exercise on a consistent basis. After 15 months of testosterone therapy, his weight had increased to 228 pounds (BMI, 37 kg/m^2). Follow-up total cholesterol levels over the 15 months (in chronological order) were 216, 231, and 252 mg/dL, with corresponding triglyceride and HDL cholesterol levels of 386, 88, and 202 mg/dL and 24, 38, and 29 mg/dL, respectively.

In general, transgender individuals are more likely to be overweight or obese compared to cisgender individuals (17). This patient developed metabolic syndrome with a dramatic increase in body weight of 50 pounds over 18 months, elevated triglyceride levels, and reduced HDL cholesterol. This case demonstrates the potential adverse metabolic effects/weight changes associated with testosterone therapy. This case also highlights the challenge in getting patients with obesity to make real lifestyle changes regarding nutrition and exercise. The Endocrine Society has published a guideline on the assessment, treatment, and prevention of pediatric obesity (18). The patient in this case did eventually begin to exercise on a semiregular basis and lost a modest 13 pounds.

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