

Gender Dysphoria in Adolescents

Ergenlerde Cinsiyet Hoşnutsuzluğu

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ABSTRACT

The incompatibility of genetically and biologically determined gender at birth and gender identity is defined as gender dysphoria (gender discontentment). Although it is seen from childhood, this picture is aggravated in adolescence when secondary sex characteristics develop. Therefore, the individual should be evaluated with the DSM-V diagnostic criteria, and after obtaining the necessary medical consents, puberty should be suppressed with GnRH agonists, which is a reversible treatment, and the next step, puberty induction, should be applied in patients with medical indications. For sex-changing surgeries, rushing should be avoided as it is completely irreversible, and the subject should be considered in detail. In case of an indication, all fertility options should be presented in detail before the operation. In addition to all these, stigmatizing adolescents with sexual dysphoria should be avoided for the continuation of healthy generations, and psychological support should be provided to these individuals due to the psychopathological conditions accompanying them at every stage of treatment.

Keywords: Gender, dysphoria, adolescent

INTRODUCTION

Gender identity is an important component of our sense of identity that determines who we are. The individual perceives his body and self with certain sexuality and directs his emotions, attitudes, and behavior in accordance with this sexual identity. Gender identity determines which gender an individual perceives himself in his inwardness. As a part of healthy sexual development, harmony between biological sex and gender identity is important. Adaptation problems in adolescents can lead to sexual discontentment. Gender

Öz

Doğumda genetik ve biyolojik olarak belirlenmiş cinsiyet ile cinsiyet kimliğinin uyuşmaması cinsiyet disforisi (cinsiyet hoşnutsuzluğu) olarak tanımlanmaktadır. Çocukluk yaşlarından itibaren görülmekle beraber sekonder seks karakterlerinin geliştiği ergenlik döneminde bu tablo ağırlaşmaktadır. Bu nedenle DSM-V tanı kriterleri ile birey değerlendirilmeli gerekli tıbbi onamlar alındıktan sonra geri dönüşümlü bir tedavi olan GnRH agonistleri ile önce puberte baskılanmalı ve tıbbi endikasyon konulan hastalarda bir sonraki aşama olan istenen cinsiyet yönünde puberte indüksiyonu uygulanmalıdır. Daha sonraki aşamada ise uygun vakalarda cinsiyet değiştirici ameliyatlar yapılmaktadır. Bu ameliyatlar tam olarak geri dönüşümsüz olup uygun endikasyonlar açısından çok titiz davranılmalı ve operasyon kararı için acele edilmemelidir. Bu konuda tam bir konsensus sağlanmalıdır. Ameliyat kararı alınan hastalar için operasyon öncesinde doğurganlık ile ilgili tüm seçenekler ayrıntıları ile sunulmalıdır. Tüm bunların yanında sağlıklı nesillerin devamı açısından cinsel disforisi olan ergenleri yaftalamaktan kaçınılmalı ve bu bireylere tedavinin her aşamasında eşlik eden psikopatolojik durumlar nedeniyle psikolojik destek sağlanmalıdır.

Anahtar Kelimeler: Ergen, cinsiyet, hoşnutsuzluk

Dysphoria (GD) is a concept that indicates the incompatibility between the biological sex determined at birth and gender identity, dissatisfaction with the body, intense desire to have the body characteristics of the opposite sex, and the desire to be treated as the opposite sex. This situation, which has been observed in every society where sexuality is defined only with the concept of biological sex, has not been defined for years. It has often been defined as a pathological condition or a disorder caused by hormonal effects. Increasingly, with the effects of studies on this subject, GD seen in adolescents or adults has started to be defined as a mental condition, not a pathological

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disease. The well-being of mental and physical health, in the definition of health, will guide in GD. This review was organized to discuss the issue of approach to adolescents with GD in light of current research and to share suggestions (1-4).

Terminology

The innate gender and sexual identity of the man are created by the interactions between anatomical, physiological, psychological, and sociocultural influences. To understand the subject further, it is beneficial to mention some terms produced as a result of these interactions and summarized in Table 1 (5,6).

Definition

The concept of gender dysphoria is a new definition according to DSM-V, and it has become a more accepted and respected definition because it is a non-stigmatizing term that expresses discomfort rather than a disorder or disease. These criteria guide the diagnosis. Gender Dysphoria in Adolescents is diagnosed according to DSM-V Criteria summarized in subtitles A and B in Table 2 (6).

Epidemiology

While the ratio of boys with sexual dissatisfaction to girls ranges between 3/1 and 6/1 before puberty, the ratio of women with sexual dissatisfaction to men after puberty increases to the ratio of 2/1 (7). The reason for this increase in women is thought to

be due to the changes in secondary sex characteristics during adolescence (8).

The prevalence of female and male transgenderism in the world and our country is not known exactly. Epidemiological studies on this subject are very few. Besides, depending on the cultural elements, revealing the sexual identity exterior to the normative limits can be met with oppression. According to the report of The World Professional Association for Transgender Health (WPATH), the prevalence of GD is broad. WPATH, reported the ratio of female transgenders between 1 / 30,400 and 1 / 200,000, and the rate of male transgenders between 1 / 11,900 and 1 / 45,000 (9).

In population-based studies between 2012 and 2017, the prevalence of transgender adolescents and adults ranged from 0.5 to 1.8 percent, and it was similar in males and females with a specified gender (10,11). In a school study by Rider et al., 2.7% of the adolescent age group participants defined themselves as transgender or having sexual diversity (12). As sexual diversity is a part of acceptable social norms, the accuracy of epidemiological data will increase.

Etiology

The exact causes are not known etiologically. Regarding the endocrine concerns, any differences were not reported in circulating sex steroid levels between transgender and non-

Table 1: Gender Terminology

Biological sex	Gender determined at birth by chromosomes, internal and external genitalia
Gender identity	An individual’s description of himself/herself as male, female, or a combination of both sexes, or the absence of feelings belonging to both genders (third gender)
Transgender	Umbrella term used to describe individuals whose gender identity is different from the gender determined at birth
Transgender male	Person of masculine gender identity assigned as a female gender at birth
Transgender female	A person with a feminine gender identity whose gender determined at birth is male
Gender diversity	A definition that accepts gender identities as a spectrum and replaces “gender mismatch” which has negative and exclusionary connotations
Gender dysphoria	Incompatibility between the person’s biological sex and gender identity
Sexual orientation	The gender the person is physically and emotionally attracted to

Table 2: Gender Dysphoria in Adolescents According to DSM-V Criteria

A- For the diagnosis, it should take at least 6 months and there should be a distinct discrepancy between the sexual identity that the person lives/expresses and the existing sexual identity. However, at least 2 of the following items should accompany.
1. There is a significant conflict between the sexual identity that the person experiences / expresses and their primary and / or secondary sexual characteristics
2. Desiring to get rid of primary and / or secondary sexual characteristics (or wanting to prevent the development of expected secondary sexual characteristics in young adolescents) since there is a significant inconsistency with the sexual identity that the person experiences / expresses
3. Desire the primary and / or secondary sexual characteristics of the other sex
4. Highly wanting to be of the other gender (or a different option from the sexual identity set for them)
5. Too much desire to be treated as if they were from the other gender (or a different choice of sexual identity set for them)
6. Highly believing in having feelings and reactions of the other gender (or specific choice of a different sexual identity for them)
B- It should cause clinically significant distress or impairment in social, educational, and other important areas of functionality

transgender individuals in research. It has been suggested that psychological, social, and biological factors are effective together in the development of GD (13).

In studies performed in individuals with congenital adrenal hyperplasia (CAH), GD was more common in individuals with the CYP21A2 mutation accompanied by virilization but without sexual development disorders. In a meta-analysis of 250 patients diagnosed with CAH, approximately 95% of women with 46, XX 21-hydroxylase deficiency and virilization did not have any GD symptoms, only 5.2% of these patients developed sexual dysphoria and defined themselves as a transgender male. Therefore, although there is not an obvious correlation, it is thought that androgens may have a role in the prenatal and postnatal periods since it is seen more than expected compared to normal prevalence in that study (14).

In some studies, psychological factors such as separation anxiety in children and GD were reported to be correlated, and more psychopathological conditions were reported in children and adolescents referred to sexual identity clinics compared to their peers in the general population, while other studies reported that these factors are not a cause but an effect in gender variability (15,16).

In a twin study based on the questions of the Child Behavior Checklist (CBC) asked mothers in records, it was found that transgender behavior or desire to be of the opposite sex was higher in female twins (17).

According to the maternal immunization hypothesis, anti-male antibodies (against male-specific antigens on the Y chromosome) of the mother develop in each pregnancy of a male fetus, and as a result, the male brain development of the fetus is affected by an immune reaction, increasing the risk related to sexual orientation. In this study, although the number of cases was limited, it was stated that those with different sexual preferences had a later delivery order (18).

In the study of Hoekzema et al., one of the neuroimaging studies in adolescence, there was only a difference between genders in terms of brain volumes, there was no difference between groups with and without GD for both genders, but subtle differences were found in gender-dependent dimorphic structures between adolescents with and without GD (both those who received medical treatment or not) (19).

Despite all these studies, the etiology has not been fully elucidated yet. There are few studies on this subject and more studies are required.

Treatment options

Appropriate treatment approaches and management are important after the diagnosis of gender dysphoria in adolescents. These patients should be evaluated with a multidisciplinary approach. Management principles in WPATH SOC (World Professional Association for Transgender Health Standards of Care) can be guiding. These treatments consist of puberty suppression therapy, sex-affirming hormone therapy, surgical interventions, and psychiatric support (9).

Puberty Suppression Therapy

Puberty suppression treatment with GnRH (gonadotropin-releasing hormone) agonists such as leuprolide, histrelin, goserelin, and triptorelin should be initiated in adolescents with sexual dysphoria that become more aggravated with the onset of puberty and do not have any psychological or other medical problems. One advantage of this treatment is that it is reversible. After this stage, the adolescent gains time regarding whether he or she wants other treatments. Therefore, the mental capacity of the adolescent to give consent and the necessity of this treatment should be confirmed by the mental health specialists. However, to apply pubertal suppression treatments in adolescents, it is reported that puberty should reach at least Tanner Stage 2 and the functionality of the adolescent in psychological, medical, and social areas should be stable enough. During the application of these treatments, physical development should be monitored by a pediatric endocrinologist by measuring height and bone density (20,21).

GnRH Analogs

GnRH analogs have been used for about 40 years in the treatment of precocious puberty to delay puberty (22). Due to this feature, it is preferred in gender dysphoria with its effect on delaying secondary sex characteristics. The main GnRH analogs are summarized in Table 3, and they act by desensitizing the receptors 10 days after one and two doses. Today, agonists are mostly preferred because there is not enough evidence regarding the reliability of antagonists (23-25). With GnRH analogs, secondary sex characteristics that are slightly developed may regress and there will be a

Table 3: GnRH analogs used in puberty suppression treatment

GnRH Agonists	Dosage and method of administration
Histrelin acetate	Subcutaneous implants are used in children aged 2 years and above, 50 mg implant placed surgically every 12 months. It secretes about 65 mcg per day for 12 months.
Leuprolide acetate (leuprorelin)	Intramuscular depot and subcutaneous forms are available. The posology may vary according to the forms. Some forms are applied once a month, every 3 months, and every 6 months.
Triptorelin pamoate	Intramuscular depot injections Available forms 3.75 mg every 28 days 11.25 mg every 3 months 22.5 mg every 6 months

pause in the next pubertal phases. While the breast tissue in girls becomes atrophic and menstruation stops, in boys, virilization pauses and testicular atrophy develops. In the early pubertal period, treatment with GnRH analogs temporarily impairs spermatogenesis and oocyte maturation. Since most adolescents want preservation of fertility, delayed initiation or temporary suspension of GnRH analogs can be considered as an option for gamete maturation. However, this is not a highly preferred method as mature gametes will be present in the late stages of puberty when secondary sex characteristics will already be developed. It should be informed that this situation is reversible. However, the time required for adequate sperm production is not known exactly after this drug is stopped. Spermatogenesis (semenarche) has been reported in males 0.7-3 years after GnRH withdrawal. Since there are not enough studies on this subject in girls, it should be noted that there is not adequate data about the time of spontaneous ovulation or ovulation induction. When medical treatment is in the late phases of puberty, the option of freezing the sperms can be considered. New techniques for cryopreservation of oocytes, embryos, and ovarian tissue are still evolving. Patients should be informed about these techniques and fertility protection (6,26-28).

Some side effects can be seen during the use of GnRH analogs. Arterial hypertension can be seen in some girls during treatment. For that reason, blood pressure monitoring is recommended before and during treatment (29). There are insufficient data on the effects of GnRH analogs on brain development. However, in some animal experiments, it has been shown that GnRH analogs may have effects on cognitive functions such as spatial orientation, learning and memory (30). Although GnRH analogs do not cause a change in the body mass index standard deviation score in patients with GD, they may cause an increase in fat mass and a decrease in lean body mass percentage (31). GnRH analogs may also cause a decrease in bone mineral density: calcium / D vit. Supplementation may be beneficial. A 6-year observational study evaluated bone mineral density (BMD) in 34 transgender adolescents (15 MTF, 19 FTM). A GnRH agonist was started at a mean age of 14.9-15 years, then, cross-sex hormones were started at the age of 16.4-16.6 years, and a gonadectomy was performed at the age of 18. During the 6-year observation period, regional BMD Z-scores tended to be decreased, which is more pronounced in MTF (0.8-1.4) individuals than in FTM (0.2-0.3) individuals (32). Because of these side effects, patients should be monitored at certain intervals summarized in Table 4 (6).

Sex affirming Hormone Therapy

If a mental health professional experienced in gender dysphoria states that gender dysphoria in the adolescent is persistent,

and if there is no social or medical condition that prevents treatment, sex-affirming hormone therapy can be started. The adolescent must have sufficient mental capacity to anticipate the consequences of treatment, which is partially irreversible, to weigh the benefits and risks, and to give informed consent for this treatment. This is 16 years of age for most adolescents. The adolescent must be informed about the loss of fertility and fertility options. If the adolescent is not of the appropriate age in terms of the legal processes, legal consent should be obtained from the family or the guardian. An experienced endocrinologist or clinician must approve the indication for sexual hormone therapy in patients with an indication for treatment before pubertal induction is initiated. Besides, the adolescent should not have any contraindications that prevent treatment (6,9,33).

Pubertal induction protocol

In transgender women, exogenous 17-beta estradiol is required for the feminization of adolescents with gender dysphoria who were assigned as male at birth. Estradiol is available in formulations such as intramuscular, peroral, and transdermal injection. Adolescents generally well-tolerate these forms. The purpose of this treatment is reduction of male-pattern hair, ensuring breast development, maintaining female-type voice, gaining elasticity of the skin, decreasing testicular volume, and preventing male-pattern musculoskeletal development. Although the duration may vary from patient to patient, the effects start between 3-6 months on average and the maximum effect can be reached between 2-3 years. These features can be partially reversible when the drug is discontinued (6,9,21,31,32,34,35).

Similarly, sex-affirming hormone treatments are applied in transgender men, and the general principle is to change the secondary sex characteristics (36). Clinicians prefer testosterone preparations used parenterally or transdermally to provide laboratory values in the range specific to normal men, and a serum level of 320-1000 ng/dl is accepted as the target value (37). The duration of the expected effects varies according to the effect. The onset of cessation of menstrual cycles, vaginal atrophy, and clitoral growth may vary between 1-6 months, and the maximum effect is around 1-2 years. The deepening of the voice, the increase of hair growth on the face and body, and the increase in muscular mass start between 6-12 months, and the maximum level can be reached between 1-5 years. Although studies have shown that the preparations used for treatment are effective and safe at physiological doses, some side effects can be seen during the use of these hormones, and patient follow-up is important according to the follow-up protocol shown in Table 5 (3,38,39).

Table 4: Basic Follow-up Protocol during Pubertal Suppression

Anthropometric measurements: weight, height, blood pressure, Tanner staging	Every 3-6 months
Laboratory: LH, FSH, E2 / T, 25OH Vitamin D	Every 6-12 months
Bone density (DXA), bone age	Every 1-2 years

Table 5: Basic Monitoring Protocol during the Sex Hormone Treatment

Anthropometric measurements: weight, height, blood pressure, Tanner staging	Every 3-6 months
Laboratory: Complete blood count (transmen), liver tests, lipids, PRL (transwomen), testosterone, and estradiol	Every 6-12 months
Bone density (DXA), bone age	Every 1-2 years

Gender Reassignment Surgery

Surgical treatment, especially genital surgery, is the final and delicate step that needs to be considered and decided very well since it is completely irreversible during the gender transition period. While many individuals with gender dysphoria only want to continue with hormone therapy, surgical treatment is indispensable for some people. In the presence of persistent gender dysphoria that meets the diagnostic criteria, if the individual has used sex-affirming hormone therapy for 1 year and is satisfied with the new gender role during this period, gender-changing surgeries can be applied. Although the specified surgery varies according to the age of adulthood in countries, it is usually around the age of 18. The necessary consents and information should be provided in detail, and there should be no biological or mental illness that prevents this treatment. While operations such as mammoplasty, penectomy, and orchiectomy are performed in transgender women, subcutaneous mastectomy, hysterectomy/ovariectomy, metoidioplasty /phalloplasty, vaginectomy, scrotoplasty, testicle, and erection implantation can be performed in transgender men (6,9,20,40).

In a meta-analysis that compiled 28 studies involving 1833 transgender patients (1093 transgender women, 801 transgender men), it was seen that individuals who received gender-affirming hormone treatments achieved significant improvements in quality of life and psychosocial assessments, gender dysphoria symptoms, and sexual functions. More standardized studies will provide a clearer understanding of the subject since the same standard tests were not applied in all studies, the difference in statistical methods, and the absence of control groups (41-43).

Psychological Treatment

Children and adolescents diagnosed with GD frequently have comorbidities with one or more psychiatric disorders. Studies have reported that the most common accompanying problems are being exposed to harassment, depression, self-harm behavior, and suicide attempts. In a study conducted using DISC (Diagnostic Interview Schedule for Children), which is a structured interview technique, no psychiatric disorder was found in approximately 68% of the cases, while one or more psychiatric disorders were found in approximately 32%. These have been identified as anxiety disorders, mood disorders, and disruptive behavioral disorders (15,44). Due to these accompanying comorbid diseases, adolescents should be provided with the necessary psychological support during the diagnosis, treatment, and follow-up stages of gender dysphoria.

Legislation in Turkey

In 1988, for the first time in Turkey, the issue of gender change became regulated by a paragraph added to Article 29 of the

Civil Code. In 2002, a more detailed regulation on gender change was made in the 40th article of the Turkish Civil Code numbered 4721. This regulation states: "Anyone who wants to change his or her gender can request the court to allow the gender change by applying in person. However, for permission to be granted, the applicant must be over the age of eighteen and not be married; he/she should also be a transgender and must certify the necessity of gender change in terms of mental health and his constant lack of reproductive ability with an official health board report from a training and research hospital. If an official medical board report confirms that a sex reassignment surgery in accordance with the purpose and medical methods has been performed depending on the permission given, the court decides to make the necessary correction in the civil registry." The applications of transgender individuals are considered within the scope of this article (45). Although the constant deprivation of reproductive ability in terms of the protection of fertility is a loss of rights, article 11, which was published in the Official Newspaper numbered 27513 in 2010, stating that the reproductive cells can be stored before operations where fertility loss may occur, will prevent loss of rights to some extent until a new regulation. Since it is not covered by general health insurance, it is far from being accessible (46).

CONCLUSION

If adolescence, which is a psychosocially turbulent and challenging process, is accompanied by gender dysphoria, this period becomes even more troublesome. These individuals should be approached in a multidisciplinary manner and the necessary psychological support should be provided. Family, community, school, and health professionals should cooperate to provide these individuals with the necessary support. For this, the awareness level of society about sexual health and different sexual orientations should be increased. These young individuals, who are the future of society, should be established without stigma and their choices should be accepted as not a disease.

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