



# Transsexualism — diagnostic and therapeutic aspects

## Transseksualizm — aspekty diagnostyczne i terapeutyczne

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### Abstract

Gender identity disorder (GID, transsexualism) is a multidisciplinary problem of an unclear aetiology. Although the diagnosis of GID is generally established by psychiatrists, the diagnostic team always includes an endocrinologist, who is responsible for hormonal therapy. Hormonal therapy is the first step in the sex reassignment procedure and requires careful monitoring in the initial phase and in later years of treatment.

In this paper we review the latest aspects of the diagnosis and treatment of transsexualism and the most common complications of hormonal intervention. (*Pol J Endocrinol* 2010; 61 (4): 412–416)

**Key words:** gender identity disorder, transsexualism, diagnosis, hormonal therapy

### Streszczenie

Zaburzenie tożsamości płciowej ([GID, *gender identity disorder*], transseksualizm) jest problemem wielodyscyplinarnym o słabo poznanej etiologii. Chociaż diagnoza GID jest zasadniczo ustalana przez psychiatrę, w skład zespołu orzekającego zawsze wchodzi endokrynolog, który odpowiada za prowadzenie terapii hormonalnej. Jest ona pierwszym etapem tak zwanej procedury zmiany płci i wymaga skrupulatnego monitorowania w okresie wdrażania, ale także w trakcie jej wieloletniej kontynuacji.

Autorzy zaprezentowali współczesne aspekty diagnostyki i terapii przypadków transseksualizmu oraz najczęstsze powikłania interwencji hormonalnej. (*Endokrynol Pol* 2010; 61 (4): 412–416)

**Słowa kluczowe:** zaburzenie identyfikacji płciowej, transseksualizm, diagnoza, terapia hormonalna

### Introduction

Gender identity is one of the most important things in everyone's life. The individual's sex is determined by the genotype, phenotype (including gonadal sex — determined by the internal and external sex organs), endocrine and metabolic status, psyche, and birth certificate sex designation (social sex). Among these "types" of sex, it is the individual's psychological sex that determines his or her gender identity.

Gender identity disorder (GID), often referred to as transsexualism, may be defined as a discrepancy between psychological sex and the morphological, biological, and social sex, which is often perceived as "non-self" and belonging to the opposite sex [1].

The available data show that the first sex reassignment surgeries in patients with GID were performed in the 1920s. Hormonal therapy to complement surgery was not introduced until 1953 (the case of Christine Jorgensen, Denmark). The first male-to-female sex re-

assignment surgery in Poland was performed in 1963 at the Polish Railways Hospital in Międzyzylesie while the first female-to-male sex reassignment surgery in Poland was performed in 1983.

According to ICD-10, the diagnosis of transsexualism requires the following criteria to be met:

- the desire to live and be accepted as a member of the opposite sex, usually accompanied by a wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatment.
- the transsexual identity has been present persistently for at least two years.
- the disorder is not a symptom of another mental disorder (e.g. schizophrenia) or a chromosomal abnormality.

The highest reported prevalence rates of GID are 1:12,000 for male-to-female (MTF) GID and 1:30,000 for female-to-male (FTM) GID [2], although data from New Zealand suggest an even greater scale of the problem



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(1:3639 and 1:22,714, respectively) [3]. Of all the cases of transsexualism manifested in childhood and adolescence, only 2.5–20.0% persist into adulthood [4].

A distinction should be made between transsexualism and transvestitism. In the latter, the affected individual has the desire to experience membership in the opposite sex (most commonly through clothes) but does not desire a permanent sex change.

## Aetiology

Little is known about the pathogenesis of transsexualism. The possible causes include an interaction of mental, psychological, and somatic (organic) factors. The significance of the latter is emphasised by the fact that even the earliest attempts to exert an external influence on children (in the first year of life) have proved ineffective as a therapeutic approach [4, 5]. At the same time a more frequent occurrence of emotional disorders, behavioural disorders, and other mental disorders in transsexual persons has been demonstrated [6].

The hormonal profile of transsexuals does not differ significantly from the hormonal profile typical of the general population. Nevertheless, it was believed that the development of this disorder might be associated with a hormonal imprinting of the brain in the foetal period. This “masculinisation” was believed to be caused by abnormal maternal levels of hormones. However, based on the example of individuals with abnormalities of sexual development with the 46 XY karyotype, it was shown that prenatal exposure to androgens does not determine male gender identity [7]. Others suggested the possibility of hormonal resistance limited to the brain tissue as they did not observe any predisposition for transsexualism in women with androgen resistance syndrome [8, 9]. Data supporting the existence of central nervous system differentiation in congruence with the psychological sex have been known for a very long time [10]. Attempts to explain the nature of transsexualism were also made on the basis of the theory of psychoanalysis and the theory of learning, examining conflicts between the mother and child, investigating psychological traumas, indicating the causative role of the parents, and their desire to have a child of the opposite sex.

## Diagnosis

According to DSM-IV-TR (*The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text-Revised*), two components must be present to make the diagnosis. Firstly, there must be evidence of a strong cross-gender identification, which is the desire to be or the insistence that one is of the other sex. This cross-gender identification must not merely be a desire for any per-

ceived cultural advantages of being the other sex. There must also be evidence of persistent discomfort about one's assigned sex or a sense of inappropriateness in the gender role of that sex. Transsexualism cannot be diagnosed if the individual has a concurrent physical intersex condition (e.g. androgen insensitivity syndrome or congenital adrenal hyperplasia). Secondly, to make the diagnosis there must be evidence of clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Transsexualism may also be suspected in children. Preoccupation with activities typical of the sex opposite to the individual's biological sex most commonly becomes evident between 2 and 4 years of age. In most cases these phenomena subside during puberty. In adults the disorder may be a continuation of a previous condition or develop *de novo*. Also, in the latter case spontaneous remissions have been reported.

It is currently believed that the diagnosis of transsexualism should only be made by a psychiatrist. The differential diagnosis must include, among other abnormalities, other personality disorders, schizophrenia, and paranoid syndromes.

## Treatment

The sex reassignment procedure, consisting of hormonal therapy and surgery, is one of the management options in transsexualism. Although it does not guarantee therapeutic success, it is preferred by the patients. Alternatives include psychiatric counselling (individual, family, marriage counselling) and psychotherapy, which may be offered to both children and adults with GID.

The moment in which the sex reassignment procedure in GID should be initiated remains controversial [4]. According to some clinicians (and many patients), delaying the sex reassignment decision increases the risk of neuroses, depression, or suicidal attempts [11]. On the other hand, due to the possibility of remission during puberty, the current guidelines do not recommend early initiation of hormonal therapy [12].

Undisputable advantages of early, peripubertal initiation of treatment include the greatest sensitivity of the target organs to hormonal therapy and the avoidance of voice change, and development of the breasts and of the appearance of the typical pattern of hair growth. The drawback is greater complexity of the surgery in MTF GID patients undergoing early hormonal treatment. One should, however, remember the considerable variability of the moment of reaching psychosexual maturity, when decisions about the selection of the gender are made in an informed manner.

If treatment is to be conducted in a minor, it should be commenced at the first signs of puberty (Tanner stage

2/3) after confirming pubertal levels of sex hormones [12]. Before the initiation of hormone therapy the patient must be fully aware of the consequences of suppression treatment and the effects of the sex hormones (characteristic of the preferred sex) he or she is going to be administered. The patient should also be informed about reproduction problems after the treatment and the limited data on the reversibility of the changes caused by the suppression of gonadotropin secretion. One of the arguments against suppressing puberty in transsexual minors is the potential possibility of disorders of gender identity formation [4].

According to the standards adopted by the World Professional Association of Transgender Health (WPATH), each adult should meet the following criteria prior to the initiation of hormone therapy:

- the patient should meet the DSM-IV-TR or ICD-10 diagnostic criteria;
- the patient should be free from mental disorders that might interfere with the diagnostic or therapeutic process;
- the patient should be aware of the expected results of treatment and the benefit-to-risk ratio;
- the patient should have real-life experience living as the preferred gender for at least 3 months or should have undergone psychotherapy for a period prescribed by a psychiatrist or for at least 3 months.

The readiness criteria for hormone therapy in adults are as follows:

- the patient has functioned in the new role during real-life experience or psychotherapy;
- the patient has made beneficial changes in coping with identified problems leading to improving or continuing stable mental health;
- there is a chance for the patient to use hormone therapy in accordance with the general principles.

The suppression of sex hormone secretion is achieved by using long-acting GnRH analogues. The much less commonly used regimens are based on progestins, antioestrogens, and antiandrogens. Hormone therapy is generally initiated after the age of 16 years.

The aim of the hormone therapy, which is carried out in parallel with suppression therapy, is to achieve physiological levels of sex hormones of the preferred gender. The treatment regimens do not differ significantly from those used in hypogonadism. In young patients with the diagnosis of FTM transsexualism, the risk of growth suppression by androgens is taken into account (which is why oxandrolone is the preferred agent).

The standard doses of male sex hormones used in the management of transsexualism are as follows: 160–240 mg/d p.o. for testosterone undecylate (Undestor, Testocaps), 100–200 mg i.m. q2w or 50–100 mg i.m. qw

for testosterone heptanoate (Testosteronum prolongatum), 1000 mg for testosterone undecylate i.m. q12w (Nebido), 2.5–10 g/d for testosterone 1–2% gel (Androtop, Tostran), or 2.5–7.5 mg/d for testosterone patches. Testosterone levels should be monitored: in the middle of the interval between the hormone injections (for testosterone heptanoate), prior to the next injection (for testosterone undecylate), at any time point after one week of using the transdermal formulation, and 3–5 hours following the intake of the oral formulation of testosterone undecylate. The concentration of testosterone should be within 350–700 ng/dL, and that of estradiol below 50 pg/mL. In MTF transsexualism, estradiol is used at the dose of 2–6 mg/d p.o., 0.1–0.4 mg biw in the transdermal formulation, or 2–20 mg i.m. q1w–q2w. The aim is to achieve estradiol levels below 200 pg/mL (734 pmol/L) and total testosterone levels below 55 ng/dL (1.9 nmol/L). Oestrogen therapy in MTF transsexualism may lead to growth limitation, which may be a plus side.

The first effects of therapy in the form of reduced libido and a decrease in spontaneous erections may appear as early as within 4 weeks, while fat redistribution, muscle mass reduction, and changes in the appearance of the skin are observed within 3–6 months of treatment initiation. A decrease in testicular volume and growth of the breasts may be expected within a similar timeframe, which is why breast augmentation surgery is not generally considered before the lapse of 2 years of oestrogen therapy. Semen production and terminal hair growth may not decrease until 3 years of treatment. In MTF transsexualism the following antiandrogens are commonly used: spironolactone 100–200 mg/d and cyproterone acetate 50–100 mg/d.

During the first year of hormone therapy, follow-up medical examinations should be conducted every 3 months. They should include an anthropometric assessment, sexual maturation assessment, blood pressure measurement, and determination of gonadotropin, testosterone and estradiol levels.

In subsequent years the frequency of visits may be reduced to 1–2 annually. Laboratory monitoring, in addition to full blood counts, liver and renal function tests, lipid profile, and carbohydrate metabolism parameters (glucose, glycated haemoglobin), gonadotropin and sex steroid levels should also include prolactin levels in MTF transsexualism and BMD calculation if risk factors for fractures are present (particularly after conclusion of hormone therapy in gonadectomised patients). Patients with FTM and MTF transsexualism should also undergo routine screening for breast and cervical cancers (if these organs are intact) and for prostate cancer, respectively [12].

Surgical transformation of the external genitalia and gonadectomy are performed after the patient reaches

legal age. This treatment is conditional upon the patient's informed decision, feeling comfortable in the new social role, and good results of at least 12 months of hormone therapy. Experts suggest that everyday functioning as the preferred gender for at least a year (the so-called real-life experience) is a prerequisite for the decision to undergo irreversible surgery. In FTM transsexualism, hysterectomy is always considered in addition to ovariectomy [12], as this way the potential risk of endometrial cancer is reduced.

In addition to gonadectomy, surgical procedures in MTF transsexualism also include penectomy (the clitoris is formed from the glans penis), formation of the vagina from the penile skin, and formation of the labia from the scrotal skin. Excess hair is removed by electrolysis or laser treatment. FTM transsexualism is a much greater challenge for the surgical team and involves a multistage procedure. The scrotum is formed from the labia majora. Erection of the surgically formed penis requires implantation of mechanical devices. Mastectomy is performed as a standard procedure [12]. It should be emphasised that in the Polish legal environment, the real-life experience, although definitely justified from a theoretical and practical point of view, should be preceded by changing the birth certificate sex designation (which is undisputed in the case of surgical treatment).

### Side effects of hormone therapy

Many questions concerning hormone therapy of GID cannot be answered unequivocally. It has not been established whether hormone therapy should be continuous or whether it should be discontinued at some point. It is unknown whether the standard recommendations for the postmenopausal period should be implemented upon reaching a certain age in the case of MTF GID. Similarly, there are no management algorithms for FTM transsexual persons who are unwilling to discontinue therapy [13].

There have been reports, for instance, of the increased risk of polycystic ovary syndrome following hormone therapy in FTM transsexuals [14]. Such suggestions have been reported in Dutch studies [15].

There have also been reports of a significantly increased risk of venous thromboembolism (VTE) in GID [16]. The risk of VTE is much higher in MTF transsexuals taking ethinyl estradiol orally compared to individuals taking 17- $\beta$  estradiol via the transdermal route. Androgen therapy in FTM transsexuals exerts anti-thrombotic effects [17]. It should be noted that an analysis of 251 cases of transsexualism (with duration of hormone therapy of  $64.2 \pm 38.0$  months) failed to confirm the increased risk of thrombosis [18].

Although concern has been raised about the potential development of an atherogenic lipid profile during hormone therapy in FTM transsexuals, no such risk has been demonstrated in clinical observations so far [19]. The authors of a review paper on 712 cases of FTM transsexualism followed up for 29 years demonstrated elevated levels of kallikreins, endothelin-1, CRP, and homocysteine during androgen therapy (250 mg of testosterone esters i.m. q2w–q3w). No changes in insulin sensitivity, fibrinolysis parameters, von Willebrand factor, interleukin-6, arterial wall rigidity, and blood pressure have been observed [15]. The study also showed no bone mineral density (BMD) loss during treatment, while other data suggest, for example, an increase in femoral neck BMD from 1.068 to 1.109 g/cm<sup>2</sup> during two years of treatment with oestrogens in MTF transsexuals [20]. One of the recently published studies evaluating the safety of a long-acting intramuscular testosterone formulation demonstrated, over 3 years of follow-up, a reduction in cholesterol levels from  $218 \pm 47$  to  $188 \pm 42$  mg/dL unaccompanied by any changes in HDL or triglyceride levels. During the same period the subjects developed increases in haemoglobin and haematocrit (typical of androgen therapy), which were still within physiological limits [21].

The potential likelihood of increasing the risk of cancer as a result of hormone therapy remains unclear. It is noteworthy that patients with MTF GID generally receive higher doses of hormones than typical patients with hypogonadism. In addition, the fact that hormone therapy is most commonly prescribed after 50–60 years of age may be of additional significance [13].

Despite the lack of certain evidence, it is suggested that oestrogen therapy of MTF GID may stimulate the development of prolactinoma [22]. Elevated prolactin levels in MTF transsexuals are demonstrated in 1 in 5 cases, which is why these patients are encouraged to have their prolactin levels checked every 1–2 years.

As far as androgen therapy of FTM transsexuals is concerned, one must not forget about the partial aromatisation of androgens to oestradiol. Although the relationship between androgen therapy and breast cancer is uncertain, once case has been reported in an FTM GID patient with residual gland tissue after mastectomy [23]. Japanese authors analysed samples of the gland tissue collected from 186 FTM transsexual individuals in terms of previous exposure to androgen therapy. Based on the comparison of the histopathological picture, they concluded that hormone therapy did not affect the risk of breast cancer [24].

There have also been reports of prostate cancer in MTF transsexuals (the prostate is not routinely resected during sex reassignment surgery) [25] and ovarian can-

cer in FTM GID patients receiving hormone therapy (prior to ovariectomy) [26].

The side effects of hormone therapy in MTF transsexual patients also include: elevated liver enzymes, cholelithiasis, depression, reduced haemoglobin, and reduced IGF-1. The side effects seen in FTM transsexual individuals include, among others, acne, weight gain, sleep apnoea syndrome, aggression, hypersexuality, increased IGF-1, and reduced BMD following gonadectomy [27].

## Conclusions

Hormone therapy is an integral element of management in patients with gender identity disorder. The aim of the treatment is to suppress the secretion of hormones characteristic of the patient's biological sex and to achieve appropriate levels of sex hormones characteristic of the preferred sex. An important part of the procedure is a thorough analysis of the potential complications of hormone therapy.

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