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A treatment protocol for adolescents with gender dysphoria: development and evaluation

Un protocolo de tratamiento para adolescentes con disforia de género: desarrollo y evaluación

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Abstract

The use of gonadotrophin releasing hormone analogs (GnRHa) to suppress puberty in adolescents with gender dysphoria is a rather new aspect of the treatment of gender dysphoria. GnRHa are used to give adolescents time to make balanced decisions on any further treatment steps, and to obtain improved results in the appearance of those who eventually continue with cross sex hormones and gender confirming surgery. The effects of GnRHa are reversible. However, it is feared that adolescents may not be able to make this kind of treatment decisions, and there may be adverse effects on their health and psychological functioning. Proponents of puberty suppression emphasize the beneficial effects of GnRHa on the adolescents' mental health, quality of life and of having a physical appearance that makes it possible for the patients to live unobtrusively in their experienced gender. From the studies that have been published thus far, it seems that the benefits clearly outweigh the risks. However, more systematic research in this area is needed to determine the safety of this approach.

Key words: *gender dysphoria, adolescence, gonadotrophin releasing hormone analogs, puberty suppression.*

Resumen

El uso de análogos del factor liberador de las gonadotrofinas (GnRHa) para suprimir la pubertad en adolescentes con disforia de género es un aspecto relativamente novedoso en el tratamiento de la disforia de género. Los GnRHa se administran a los adolescentes con el fin de proporcionarles más tiempo para la toma de decisiones sobre etapas posteriores del tratamiento, y también para obtener mejores resultados estéticos en aquellos que eventualmente vayan a proseguir con hormonas sexuales cruzadas y cirugía de confirmación del género. Los efectos de los GnRHa son reversibles. Sin embargo, preocupa que los adolescentes no sean capaces de tomar decisiones sobre este tipo de tratamiento y también que puedan existir efectos adversos sobre su salud física y psicológica. Los proponentes de la supresión puebral enfatizan los efectos beneficiosos de los GnRHa sobre la salud mental de los adolescentes, la calidad de vida y el hecho de adquirir una apariencia física que les permite vivir sin controversias en el género sentido. A partir de los estudios hasta ahora publicados, se deduce que los beneficios superan claramente los riesgos. Sin embargo, se necesitan investigaciones más sistematizadas en esta área para poder determinar la seguridad de este abordaje.

Palabras clave: *disforia de género, adolescencia, análogos del factor liberador de las gonadotrofinas, supresión puberal.*

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Introduction

Gender dysphoria (GD) is characterized by distress due to an incongruence between experienced gender (gender identity) and natal sex [1]. Individuals

who suffer from extreme forms of GD usually seek gender confirming treatment (GCT). This may consist of cross-sex hormone treatment and feminizing or masculinizing surgery. Clinicians often use the Standards of Care of the World Professional Association for Transgender Health (WPATH). Hormone treatment guidelines have been formulated by the Endocrine Society, which are currently under revision [2].

Adolescents with GD usually have been gender dysphoric since early childhood [3]. For them, puberty is a stressful experience and puberty may have a strong negative impact on their emotional and social functioning, and even on their performance in school. Therefore, the suppression of puberty, followed by gender confirming hormonal and surgical treatment may have great benefits.

Protocol development

The practice of puberty suppression in young adolescents has, in steps, been developed by the team at the Amsterdam Gender Identity Clinic, The Netherlands. Clinical observations, made in the late 1980s, lead to the first step. First, it was clear that, despite many years of psychotherapy, which was then the primary approach to GD in adolescence, the GD hardly ever resolved. Second, many of the adolescents' problems (e.g. depression) seemed to be the consequence, rather than the cause, of their GD. At the time, cross-sex hormone treatment was not offered to persons under 18 years. The Amsterdam Gender Identity Clinic therefore changed its treatment policy.

First change in treatment policy; cross-sex hormones from 16 years old

The first treatment protocol developed at the Amsterdam Gender Identity Clinic consisted of a staged hormonal treatment in patients ≥16 years old. Natal males were initially given antiandrogens and if they responded positively to this first phase, estrogens were added. Natal females received progesterone first and then androgens. The diagnostic procedure that was followed for adults was adjusted to select good candidates for this staged hormonal treatment. The family was more involved, there was more extensive psychological testing and eligibility criteria were more strict. The eligibility criteria were age 16 years or older, a clear GD since early childhood, persisting gender dysphoria upon entering puberty, no comorbidities or other circumstances that could interfere with the diagnostic work or treatment, support from parents or caretakers, and a good understanding of the effects of the treatment.

Before treatment started, ample attention was given to the effects and limitations of all treatment steps (limitations of surgery included), and to factors that could seriously jeopardize treatment (for example, smoking) to enable a truly informed consent. Treatment decisions were always taken by the whole team.

Over the years, the protocol was evaluated in a number of follow-up studies, using interviews and questionnaires. Treatment appeared to result in the disappearance of GD, and none of the participants regretted undergoing treatment as assessed by interviews and questionnaires [4,5]. The psychological and social functioning of the adolescents also seemed to be comparable to that of their peers. In a group of 27 applicants for treatment who were not accepted for early treatment or withdrew from the diagnostic procedure, 6 pursued GCT in adulthood, usually after some other form of psychiatric treatment and some still with considerable problems such as bipolar disorder or a chaotic family situation. However, the large majority of adolescents who did not receive early treatment never reconsidered undergoing GCT [5]. When conducting these follow-up studies, it became clear that the appearance of those adolescents who not reached Tanner stage 5 (the last phase of puberty development) at the start of the treatment, was much more in accordance with the experienced gender than the appearance of individuals who were treated in adulthood. Early intervention not only seemed to lead to a better psychological outcome, but also to a physical appearance that makes being accepted as a member of the experienced gender much easier, compared with those who began treatment in adulthood.

Second change in treatment policy; addition of puberty blocking hormones.

As these first studies favored early, rather than late, interventions, the Amsterdam team decided to reduce the age limit for starting hormonal treatment. In the first protocol, the adolescents were initially treated with medications that either blocked the effects of all androgens (antiandrogens in natal males) or only suppressed menstruation (progesterone in natal females), before they received cross-sex hormones. In the second protocol the development of secondary sex characteristics was prevented in the early Tanner stages (Tanner stage 2/3). This seemed advantageous, as the adolescent would not experience the alienating effects of a body that changed in an unwanted direction. For this purpose, gonadotropin-releasing hormone analogs (GnRHa; triptorelin) were used [6]. If treatment with GnRHa is stopped, puberty in line with the natal sex will continue to develop. In this sense the treatment is reversible. If the adolescent still wanted to start the actual GCT

when they were 16 years old, a feminizing puberty was induced in natal boys by prescribing increasing dosages of 17β-estradiol. An adult dose was given when the adolescent reached 18 years of age. In natal girls, a male puberty was induced with increasing dosages of testosterone esters. At age 18 years an adult dose was given. Further information about the endocrine treatment procedure can be found in the guidelines of the Endocrine Society [2], which are currently under revision.

After the first experience with a natal girl who responded to the treatment exceptionally well [7] it was decided to start treatment in a large number of carefully selected adolescents. In addition to the criteria that had been set for the ≥16 year olds, eligible participants now had to be at least 12 years old. Because it seemed to be important that adolescents experience some of the physical effects of puberty to make a well-informed decision on whether to suppress these effects, they had to be in Tanner stage 2-3 of their pubertal development before starting treatment. By providing extra time to allow for further exploration of the desire for irreversible interventions (cross-sex hormones and surgery) without the distress of puberty, GnRHa treatment is considered to be a diagnostic aid.

Early intervention has proven to ameliorate psychological functioning and quality of life of the young adolescent with GD during treatment and well after. In one study from the Amsterdam team that examined the first cohort of 70 candidates eligible for puberty suppression it was found that psychological functioning improved considerably during GnRH analogues treatment, but, as expected, the gender dysphoria did not change [8]. In a second study from the same team, 55 young adults were interviewed ≥1 year after surgery that was preceded by treatment with GnRHa and cross-sex hormones. It was found that the gender dysphoria had disappeared and that their quality of life was good [9]. No one regretted treatment and the participants were similar to their peers with regard to relationships, education and/or career.

So far, little is known about somatic aspects of GCT in (early) adolescence (for a review see [10]. Safety considerations are to be made on short-term as well as long-term effects. Puberty is a crucial developmental phase for bone health and may also be important for cardiovascular health in adulthood [11]. Although the short- and long-term safety of GnRHa in central precocious puberty is well documented [12], the results cannot be readily translated into adolescent transgender health care. This is because GnRHa treatment is started at an older age and generally continued until the age of 15-16 years and it is followed by a pubertal induction of the experienced, not natal, desired sex. Therefore the long-term follow-up of adults with GD who started GR in their early adolescence, is warranted.

In adolescents with GD absolute bone mineral density (BMD) values remained stable during GnRHa treatment but z-scores decreased. When cross-sex hormone treatment was started, bone mass accrual resumed [13]. When BMD development was assessed until young adulthood, however, it was found that the loss in Z-score was still partially present at the age of 22, implying a possible delay in peak bone mass [14]. To this date only one case report has been published on long term BMD development. Absolute BMD and Z-scores of a 35 year old transman, treated with GnRHa in adolescence, were in the normal range [8]. It seems advisable to periodically monitor BMD and to encourage frequent weight-bearing activities and adequate calcium intake [15].

Controversies

GnRHa treatment for young adolescents with GD is still controversial. One may wonder what causes more harm: abstaining from medical interventions or interfering medically? Those who are against the use of GnRHa stress the risk of making incorrect decisions, because in adolescence gender identity might still be fluctuating, the inability of adolescents to make far-reaching decisions and to understand the effect puberty suppression will have on their lives, potentially adverse effects of GnRHa treatment on psychological functioning, and the possibility that puberty suppression before Tanner stage 4 or 5 is medically unsafe [16,17].

Proponents of early treatment emphasize the suffering of those who had to wait for treated until adulthood, the distress and poor quality of life of adolescents who are denied treatment before adulthood and the life-long advantage of having a physical appearance in accordance with the desired gender. Abstaining from treatment might also lead to risky behaviors (for example, self-mutilation, self-medication or suicide) [18-22].

From the currently available evidence it appears that the diagnosis can reliably be made in adolescence and that a GD that seems to worsen around puberty rarely abates afterwards. A careful diagnostic procedure, together with proper treatment, has thus far resulted in good outcome with young adults who felt well prepared for GCT [9,23]. Yet, long-term follow-up studies are necessary to draw more definite conclusions. In addition to the areas that were discussed previously, there is need for MRI studies investigating the effects of GnRHa and subsequent cross-sex hormone treatment on the developing brain. However, the very few studies that were conducted so far do not suggest unfavorable effects. Clinically, ado-

lescents who have received hormone treatment in early adolescence do not seem to function very differently from their peers [for a review see [24]]. Social-emotional functioning clearly ameliorates as a result of puberty suppression [23], preventing psychopathology as a result of an absence of GD treatment. Some of the sex characteristics that are typical for the natal gender (such as a beard or breasts) do not need to be 'corrected' later in life. Not allowing adolescents to take GnRHa might result in an appearance that could provoke abuse and stigmatization. Withholding GnRHa treatment does not seem to be a neutral option. The increase in treatment centers in many countries offering this treatment reflects this thought [25-27].

Conflicts of interest

The author declares that there are no conflicts of interest.

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