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Endocrine Approach in Gender Dysphoria: The Experience in a Reference Centre

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A B S T R A C T

Introduction: Gender dysphoria (GD) is characterized by a marked discordance between the psychological perception of individual sex and the biological phenotype. In the present article, the authors aimed to analyze the clinical data of a cohort of subjects diagnosed with GD, referred to a national unit, specialized in the endocrine, psychiatric and surgical treatment of this entity.
Methods: Data about demographics and response to treatment, were retrospectively analysed in 85 subjects diagnosed with GD, who were observed in the Endocrinology Consultation, during a 12-year period.
Results: It was verified that among 85 patients included in the study, 38 (44.7%) were transgender females and 47 (55.3%) were transgender males. The number of patients seeking treatment substantially increased in the last 5 years, with an inferior age of referral in transgender males. Sixty-three patients (74.1%) started cross-sex hormone therapy, deprived of significant adverse events, and gender affirming surgery was performed in 25 patients (29.4%).
Conclusion: Our study revealed a progressively growing number of patients seeking sexual reassignment, being predominantly transgender males. The majority of subjects started hormone therapy without substantial related adverse events, corroborating that it may be considered as a relatively safe treatment. Gender affirming surgery was performed in a reasonable number of patients, which was comparable with the experience of other centers.

Palavras-chave:
Disforia de Género
Pessoas Transgénero
Sistema Endócrino

Abordagem Endocrinológica na Disforia de Género: A Experiência num Centro de Referência

R E S U M O

Introdução: A disforia de género (DG) é caracterizada por uma discordância marcada entre a perceção psicológica do sexo individual e o fenótipo biológico. No presente artigo, os autores pre-

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tenderam analisar os dados clínicos referentes a uma coorte de indivíduos com o diagnóstico de DG, referenciados para uma unidade especializada no tratamento endocrinológico, psiquiátrico e cirúrgico desta entidade.

Métodos: Foram analisados retrospetivamente dados demográficos e sobre a resposta ao tratamento em 85 indivíduos, com o diagnóstico de disforia de género, observados em consulta de endocrinologia, durante um período de doze anos.

Resultados: Verificou-se que de 85 indivíduos incluídos no estudo, 38 (44,7%) correspondiam a mulheres transgénero e 47 (55,3%) a homens transgénero. O número de indivíduos a solicitarem tratamento aumentou substancialmente nos últimos 5 anos, com idade de referenciação inferior no grupo de homens transgénero. Sessenta e três indivíduos (74,1%) iniciaram terapêutica hormonal, sem efeitos adversos significativos. Foram realizadas cirurgias de reatribuição sexual em 25 elementos da amostra (29,4%).

Conclusão: O estudo apresentado revelou um número progressivamente crescente de indivíduos a solicitarem reatribuição sexual, sendo predominantemente homens transgénero. A maioria dos indivíduos iniciou terapêutica hormonal sem eventos adversos associados substanciais, corroborando que esta poderá ser considerada como um tratamento relativamente seguro. Foram realizadas cirurgias de reatribuição sexual num número razoável de indivíduos, o que foi comparável com a experiência de outros centros.

Introduction

The definition of gender dysphoria (GD) was originally presented by Fisk in 1973, to describe individuals who experienced a profuse discomfort with the assigned or birth gender and urged for sex reassignment.[1] More recently, in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders - DSM-5 (American Psychiatric Association, 2013), the expression "gender identity disorder" was reviewed and replaced by "gender dysphoria", reflecting an alteration in the perception of the disorder, in an effort to better characterize the experiences of affected children, adolescents, and adults. According with DSM-5, the diagnosis of gender dysphoria is currently characterized as a marked difference between the gender experienced by the individual and the gender that is recognized; in children, the desire for being attributed with another gender must be present and verbalized. Additionally, it is considered as a condition that causes clinically significant distress or impairment in social, occupational and other important areas of individual activity.[2]

Few studies evaluated the prevalence of GD nevertheless, most of the data are probably underrated. De Cuypere *et al* reported the results of one of the largest studies on this subject so far, having described a significant variability in the prevalence of this entity, which was associated with the geographical location and different social characteristics of populations.[3] In adults, according with DSM-5, the prevalence of GD is respectively 0.005% - 0.014% of adult males and 0.002% - 0.003% of adult natal females, with a ratio up to 3:1 of genotypic males to genotypic females.[2]

Concerning the etiological factors, some authors suggest a biologic etiology for GD, since studies about disorders of sexual development and neuroanatomical examination have been providing evidence on an organic basis.[4-11] However, considering the small sample size of most of the studies on this topic, these assumptions must be taken with carefulness.

The objective of cross-sex hormone therapy (CHT) and gender affirming surgery (GAS) is mainly the improvement of well-being and quality of life (QoL) of these patients, together with the acquisition of phenotypic features of the aimed gender. The Harry Benjamin International Gender Dysphoria Association (HBIGDA), which is nowadays recognized as the World Professional Association of Transgender Health (WPATH), published the first clinical care guidelines in 1979. More recently, the clinical practice guidelines of the Endocrine Society and other similar recommendations as "The Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People - Version 7" (WPATH SOC7) have been presented, contributing for the standardization of treatment in these patients.[12,13] According to the referred orientations, sex reassignment is considered as a multidisciplinary treatment, which should be ideally managed by a multidisciplinary team at centers with competencies to provide diagnostic assessment, psychotherapy, real-life experience, hormone therapy and GAS.

Current research has been settling hormone therapy as a valuable and relatively safe resource in adults with GD. Murad *et al* demonstrated an improvement of about 80% in GD subjects who performed CHT, usually accompanied by GAS, regarding psychological symptoms and QoL.[14] Still, cross-sex hormone regimens can be associated with significant medical complications and several studies have been reporting short and long-term effects.[15]

Regarding GAS, the current recommendations point that surgical treatment should be performed if the subject preserves the desire of a definitive surgical change, exclusively after the development of an acceptable social role modification and in the presence of satisfactory results of hormone therapy.[13] However, in the case of adolescents, surgery is not indicated before reaching adulthood, although the decision may be made before it. Contemporary outcome studies indicate that GAS has beneficial effects on different dimensions of patients' lives, however the process of social adaptation of transsexual patients still comprises several difficulties.[16,17]

In the present article, the authors intend to report an analysis of the clinical and demographic data of a cohort of subjects diagnosed with GD and referred to a national unit, dedicated to the clinical assessment, hormone treatment and GAS in this setting.

Material and Methods

The authors performed a retrospective and cross-sectional study which included 85 subjects diagnosed with gender identity disorder and GD, observed in the Endocrinology Consultation of a reference care center between January 2004 and September 2015. No exclusion criteria were applied.

Ever since 2011, all patients were specifically referred to URGUS (Unitfor Genital-Urinary and Sexual Reconstruction of Coimbra Hospital and University Centre) in order to perform clinical evaluation, hormone therapy and GAS (minimum age of 18 years old). The URGUS consists of a reference unit of the Portuguese National Health System, which was created in November 2011

and fully accredited by Directorate-General of Health (DGS) in October 2017. It directs its activity by the values of human dignity, respect for ethics, following well-established medical, surgical and psychological practices. The purposes of URGUS include the medical treatment and GAS in cases of GD, based in protocols that follow the WPATH and the Endocrine Society Clinical Practice Guidelines.[12,13] URGUS establishes as a gateway the consultation of Sexology, carried out by a Psychiatrist or Psychologist, and after this consultation the patient initiates a sequence of specific evaluations and treatments, under the responsibility of a multidisciplinary team that integrates several specialties (Endocrinology, Urology, Gynecology, General Surgery and Plastic Surgery).

In relation to hormone therapy protocol established in the Endocrinology Consultation, transgender females initiate treatment with oral estrogen, consisting of oral estradiol (2–6 mg daily). The aim of the treatment is to ideally maintain serum estradiol at the mean daily level for premenopausal women (<200 pg/mL), and serum testosterone level in the female range (<55 ng/dL). In order to intensify anti-androgen effect, cyproterone acetate (25-50 mg daily) or spironolactone (100-200 mg daily) are added to therapy in selected patients. Regarding transgender males, intramuscular testosterone enanthate (250 mg) is generally administered every 2 weeks, and doses titrated considering testosterone blood levels in the normal age-adjusted male range and also hematocrit levels. In some cases, in order to suppress luteinizing hormone, follicle-stimulation and ovarian function, a long-acting analogue of gonadotrophin-releasing hormone (GnRH) - tripotorelin acetate 11.25 mg, subcutaneously, every 3 months - is added to therapy.

The patients were generally evaluated on a 3-months basis by a specialized doctor, depending on the period of the gender affirming process, which included clinical and analytical monitoring of therapy effects and related adverse events.

The age of clinical presentation and of admission in the Endocrinology Consultation, as well as concomitant comorbidities, the treatment performed and potential related adverse events, or complications were some of the analyzed variables.

The statistical analysis was performed using SPSS version 22.0 and a descriptive assessment of the data was carried out. Results of continuous measurements were presented as mean ± standard deviation (SD) and results of categorical measurements were numerically presented (frequency and percentages). Student's t-test was performed to evaluate normally distributed numerical data and chi-square test to analyze categorical variables. For all the analyses, level of significance was accepted as $p \leq 0.05$.

Results

A total of 85 patients were included in the sample. The baseline demographic and clinical characteristics of gender variant subjects are outlined in Table 1.

The majority of patients were transgender males (55.3% *vs* 44.7%). The average age of presentation to the Endocrinology Consultation was 29.3 ± 11.6 years, being statistically inferior in transgender males (25.4 ± 9.9 *vs* 34.2 ± 11.8; p <0.001). It was also observed that the age of clinical presentation was significantly inferior in this cluster (6.3 ± 2.1 *vs* 8.5 ± 3.8; $p = 0.005$).

Overall, 23.5% of patients were unemployed, with a higher rate seen in transgender males (14.1% *vs* 9.4%). Nearly 38% of patients were employed at time of presentation and 28.2% were students.

The presence of a psychiatric disorder was the most frequent associated comorbidity (30.5%), followed by the presence of thyroid disease (8.2%), which was identified in the Endocrinology Consultation. Concerning the family history, it is interesting to note that in 4 patients, a history of transsexuality was identified in first or second degree relatives.

Although yearly totals arediverse, there was an important increase over time in the number of persons seeking CHT (Fig. 1). The hormone treatment was initiated in 38 (80.8%) of transgender males and in 25 (65.8%) of transgender females (Table 2).

Table 1. Demographic and descriptive characteristics of study population.

Demographic data	**Transgender females**	**Transgender males**	***p***
Number of subjects	38 (44.7%)	47 (55.3%)	-
Age of clinical presentation (years)	8.5 ± 3.8	6.3 ± 2.1	0.005
Age at referral (years)	34.2 ± 11.8	25.4 ± 9.9	<0.001
Age at initiation of CHT (years)	27.7 ± 11.7	25.1 ± 7.4	0.275
Associated Diseases	**Transgender females (%)**	**Transgender males (%)**	**Total (%)**
Type 2 diabetes *mellitus*	2 (2.4)	0 (0.0)	2 (2.4)
Thyroid disease1	1 (1.2)	6 (7.0)	7 (8.2)
Neoplasia	0 (0.0)	1 (1.2)	1 (1.2)
HIV-positive	3 (3.5)	0 (0.0)	3 (3.5)
History of drug addiction	2 (2.4)	3 (3.5)	5 (5.9)
Karyotype alteration2	0 (0.0)	1 (1.2)	1 (1.2)
Psychiatric disorder	15 (17.6)	11 (12.9)	26 (30.5)
Employment status	**Transgender females (%)**	**Transgender males (%)**	**Total**
Employed	17 (20.0)	15 (17.7)	31 (37.7)
Retired	3 (3.5)	1 (1.2)	4 (4.7)
Unemployed	8 (9.4)	12 (14.1)	20 (23.5)
Student	9 (10.6)	15 (17.7)	24 (28.2)

Legenda: HIV = human immunodeficiency virus; Thyroid disease1=papillary thyroid carcinoma; Karyotype alteration2= Turner syndrome.

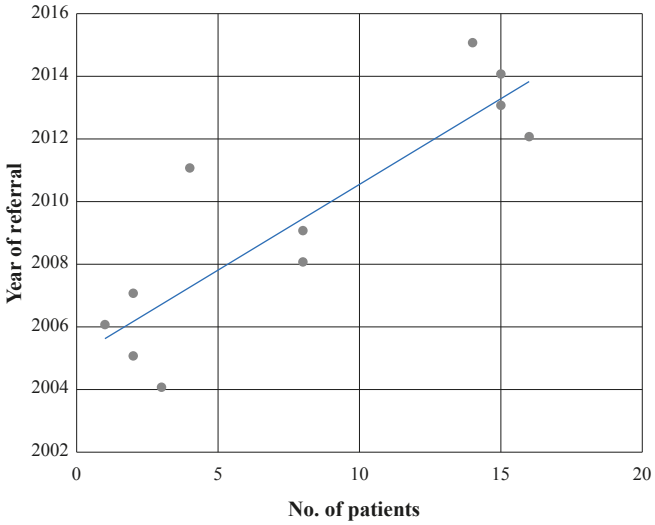

Figure 1. Number of patients presenting for cross-sex hormonal therapy between 2004 and 2015.

Table 2. Hormone therapy and reported adverse events.

	Transgender females (%)	Transgender males (%)	*p*	Total
Hormone therapy	25 (65.8)	38 (80.8)	0.115	63 (74.1)
Reported adverse events	3 (12.0)	8 (21.1)	-	11 (17.5)

Compared with transgender males, a larger number of transgender females started hormone therapy preceding their first visit to us (10.6% *vs* 2.4%), without medical supervision. In transgender females, all of the 25 subjects initiated oral estradiol therapy, with a smaller number of patients (n=11) requiring treatment with antiandrogens. Concerning transgender males, all of the 38 patients who underwent CHT performed testosterone enanthate therapy and in 22 individuals a long-acting analogue of GnRH was added to treatment.

Regarding the level of treatment-related adverse effects, they were reported in a total of 11 patients. The most frequent one was the appearance of acne associated with the administration of testosterone enanthate, followed by the occurrence of peripheral edema, related with the administration of estradiol (Table 3). In addition, it is relevant to note that there were no episodes of acute thromboembolism in any patient or other major adverse-effects.

Table 3. Specification of hormone treatment-related adverse events.

Adverse event	Formulation	No. of patients
Acne	Testosterone enanthate	7
Peripheral edema	Estradiol valerate	2
Headaches	Estradiol valerate	1
Panic attacks	Testosterone enanthate	1

Concerning the surgical treatment, this was performed in 15 (31.9%) of transgender males and in 10 (26.3%) of transgender females. It is relevant to mention that 11 of the patients included in this study had already performed at least one surgical procedure before their assessment at URGUS. In transgender females, surgeries included breast augmentations (8 patients), vaginoplasties (5 patients), orchiectomy (2 patients) and facial cosmetic surgery (1 patient). In transgender males, the most frequent surgical interventions were bilateral mastectomy (in 11 patients), total hysterectomy *plus* bilateral anexectomy (in 6 patients), vaginectomy (in 6 patients) and phalloplasty in 5 patients (Table 4).

At the end of the study, patients presented a mean follow-up of 27.24 months. A total of 21 subjects were awaiting approval for surgical intervention and 11 patients were already approved and included in the waiting list for surgery.

Table 4. Gender affirming surgeries performed in the whole cohort.

Transgender females	No. (%)	Transgender males	No. (%)
Breast augmentation	8 (21.1)	Bilateral mastectomy	11 (23.4)
Vaginoplasty	4 (10.5)	Hysterectomy *plus* bilateral anexectomy	6 (12.8)
Orchiectomy	2 (5.3)	Vaginectomy	6 (12.8)
Facial cosmetic surgery	3 (7.9)	Phalloplasty	3 (10.6)

Discussion

Gender dysphoria is an expression which labels behaviors, interests and the identity of persons who do not conform with their biological gender.

Along the past years, we have seen a growing number of patients with GD, who were included in the URGUS program, which is in line with the experience of other centers.[18,19] We believe that the rise in the amount of patients looking for therapy may be an echo of a cumulative social acceptance but, the larger information available concerning GD may also explain this observation.

There are some interesting points that we found in our experience. In some clinic-based studies, it is clear that the prevalence of transgender females is remarkably higher than of transgender males, as it was described in populations from Belgium (2.43:1), Spain (2.2:1) and Sweden (1.8:1).[3,20,21] Contrastingly, in our sample, it was observed a superior number of transgender males compared with the subset of transgender females (1.24:1). This can be considered as an interesting issue however, there are already a few reports describing that the ratio transgender females to transgender males has been dropping.[22] Still, it is obvious that straight comparisons between studies are erroneous, considering the differences on data collection methods, as well as in the criteria for documenting GD.

As in previous reports we observed that there was an extreme delay in the initiation of endocrine consultations, considering that the mean age of clinical presentation was respectively 6.3 ± 2.1 and 8.5 ± 3.8 years, in transgender males and transgender females.[23] This wide deferral in endocrine evaluation is probably related with the difficulty that patients face to reveal their sexual identity, which may lead to an overdue on initiating adequate treatment. Another interesting finding was that the average age of presentation to our department was statistically inferior in transgender males (25.4 ± 9.9 *vs* 34.2 ± 11.8; $p < 0.001$), which was comparable to the results obtained by Leinung *et al.*[19]

Also in conformity with prior studies, we did not find significant differences in the level of education between transgender females and transgender males.[18,19] However, we observed a higher number of transgender males who were students, being this data probably related with a younger age at referral of these subjects

to our center.

An additional important finding was the elevated prevalence of psychiatric disorders that were observed, which is possibly not surprising, considering the social barriers that these individuals usually face and the probability of mental health problems that prolonged dysphoria would be expected to produce. The presence of other types of associated comorbidities was also notorious, confirming the importance of an accurate medical assessment of these patients, preceding hormone treatment and GAS.

Regarding CHT, we noticed that hormone therapy for transgender males was commonly effective in reaching satisfactory masculinization. However, in transgender females, there was less facility to induce full feminization, which may also be related with a more advanced age in the introduction of hormone treatment. Therefore, this may highlight the need to start hormone therapy earlier, in order to obtain better results and reduce the consequences of dysphoria, as soon as patients present the designated criteria to start CHT.[13]

We found that at our center transgender females and transgender males had comparable risk for hormone-related adverse effects. In addition, we observed only minor adverse effects occurring in our sample and none of the patients experienced cardiovascular events. These results are consistent with preceding studies, which have proven that CHT is reasonably safe in both clusters, once hormone levels are maintained within physiological ranges.[24,25] However, the presence of risk factors as obesity, dyslipidemia or elevated serum hematocrit, raises the concern for possible cardiovascular events in these patients, emphasizing the requirement of an extensive clinical evaluation and correction of these factors when necessary.[26]

Regarding the occurrence of venous thrombosis, we did not account for any case in the present study. This was clearly inferior to the results reported by Van Kesteren *et al* who demonstrated that 6.4% of transgender females experienced deep venous thrombosis or pulmonary embolism thrombosis events during hormone therapy.[27] However, this difference may be related with our relatively small sample size and time of follow-up, which does not allow us to provide a straight incidence of morbidity rates and can be considered one of the weaknesses of the present study. Although the referred boundaries, we believe that our data may contribute to the analysis of the effects and adverse events of hormone therapy in patients with GD, especially considering that studies on this topic are still limited.

Gender affirming surgery was performed in about 30% of patients however, in a superior number in transgender males (31.9% *vs* 26.3%), being this result identical to other studies.[18,19] This may be related to some factors, for example, procedures as mastectomy and hysterectomy are in general less expensive and technically simpler than vaginoplasty. Other authors as De Cuypere *et al* also related this difference with a greater level of employability in transgender males however, this was not observed in our sample.[3]

In transgender females, breast augmentation was the most frequently performed surgery, which was probably related to the technical simplicity of the procedure. In transgender males, the most frequent procedures were bilateral mastectomies, followed by hysterectomy plus bilateral anexectomy and vaginectomy. In a recent review, Richards *et al* reported the impact of bilateral mastectomy in subjects who had concluded it as part of GAS. They demonstrated that this intervention was essential for transgender males, so that they could live safely and effectively in their reassigned gender role. Additionally, the authors verified that it acts prophylactically against distress, being also indispensable for improving QoL and global functioning in these subjects.[28] In another study, Dhejne *et al* evaluated the rates of mortality, morbidity, and criminal rate after GAS in a population-based matched cohort study. Their study found significantly superior rates of overall mortality, death from cardiovascular disease, suicide *plus* suicide attempts and hospitalizations for psychiatric disease in individuals who performed GAS, compared to a healthy control population. Accordingly, they concluded that post-surgical patients with GD should be considered as a risk group that requires long-term psychiatric and somatic evaluation.[17] In this sense, although surgery and hormone therapy mitigate some of the associated problems of GD, they are actually insufficient to reduce the high rates of morbidity and mortality observed amongst these patients, thus a long-term follow-up and improved care after GAS should be considered.

Finally, although the present study did not include an extensive number of patients, it is to our knowledge, the first Portuguese retrospective study focusing in the endocrine approach of GD, which may contribute to accomplish a more comprehensive care and personalized approach of these individuals.

Conclusion

In the last years, we observed a growing number of patients with GD who were referred to our center in order to perform hormone therapy and GAS, with the majority of them being transgender males.

The majority of subjects initiated hormone therapy without significant related adverse events, supporting that it may be considered as a relatively safe treatment. Regarding gender affirming surgery, it was performed in a reasonable number of patients, which was comparable with the experience of other centres.

We consider that although additional studies with larger cohorts of subjects and prolonged follow-up periods are essential to increase the knowledge about this entity, also a deeper awareness of society on this condition and increased collective acceptance may have the potential to improve outcomes in the setting of GD.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declararam inexistência de conflitos de interesse.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.
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Ethical Disclosures

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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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