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A European Network for the Investigation of Gender Incongruence: Endocrine Part

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ABSTRACT

Introduction: Cross-sex hormone therapy is an essential part of gender affirming treatment of transgender individuals. Studies systematically describing the physical and psychological effects of hormonal treatment of transgender persons are scarce.

Aim: The aim of the current protocol is to evaluate clinical and side-effects of cross-sex hormonal treatment in trans persons.

Methods: The European Network for the Investigation of Gender Incongruence (ENIGI) is a multicenter prospective study. Because of the relatively low prevalence of the condition and small number of specialized centers, international collaboration is warranted. Four European treatment centers, Ghent, Oslo, Florence, and Amsterdam, developed a common study and treatment protocol.

Main Outcome Measures: Outcome measures include hormonal and metabolic parameters, bone density, secondary sex and anthropometric characteristics, and physical and psychological well-being.

Results: Thus far, 333 trans women and 343 trans men have been included in the ENIGI Endocrine protocol. The study is still ongoing.

Conclusion: In recent years, the number of trans persons seeking gender affirming treatment has increased. However, well-designed prospective studies evaluating safety and effectiveness of current hormonal treatment protocols are lacking. Therefore we started the ENIGI collaboration. In this article we give a detailed description of the study protocol, objectives, and design of the ENIGI Endocrine protocol.

Key Words: Gender Dysphoria; Cross-Sex Hormonal Treatment; Prospective Cohort Study

INTRODUCTION

"Gender dysphoria" (GD) refers to the distress related to an incongruence between one's experienced gender and one's assigned gender that has been present for at least 6 months.[1] This condition has a great negative impact on physical, social, and psychological well-being and a large proportion of trans persons (but not all) desire gender affirming treatment.

For most trans individuals, hormonal treatment is an essential part of their sex change. Harry Benjamin (January 12, 1885–August 24, 1986) born in Germany, was an American endocrinologist and sexologist who was one of the pioneers treating patients with cross-sex hormones around the middle of the twentieth century. Although gender reassignment was still a matter of much debate, over half a century later hormone therapy and surgical reassignment are accepted as the mainstay treatment for gender dysphoria.[2]

Currently, endocrine treatment regimens are not standardized and include various forms, applications, and dosages of estrogens, progestins and (anti) androgens.[3] Thus far, no randomized intervention trials have been performed to determine the best treatment regimens. Furthermore, no large prospective studies have evaluated

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(side) effects of cross-sex hormone treatment (CHT) in a structured manner. The European Network for the Investigation of Gender Incongruence (ENIGI) collaboration creates a unique opportunity to perform the much-needed research in this field. The main objective of the study is to describe the clinical effects and side-effects of hormonal treatment in adults with GD. All participating centers will evaluate these clinical effects using the same standardized measurements and questionnaires.

Previously, Kreukels et al[4] presented the diagnostic protocol and psychological assessments used in the ENIGI Mental Health protocol. The close collaboration between both mental health and endocrine specialists offers a unique possibility for translational and interdisciplinary research. Furthermore, the international and multicenter approach of this study facilitates collaboration and exchange between different European expert centers. Another major advantage of this collaboration is that we can include larger number of patients in our study. This is of specific importance, because although patient numbers are increasing, GD is still a relatively rare condition.

AIMS

The aims of the endocrine part of the ENIGI collaboration is to evaluate the effects of CHT on hormonal and metabolic parameters, bone density, secondary sex and anthropometric characteristics, and physical and psychological well-being of trans persons. In this article, we present the study design and data collection procedures of the ENIGI Endocrine protocol.

SUBJECTS AND METHODS

Participating Centers

The ENIGI study is a multicenter prospective cohort study. So far, 4 West European gender identity clinics are participating in this collaboration. They include Ghent University Hospital, Belgium; VU University Medical Center in Amsterdam, the Netherlands; Rikshospitalet in Oslo, Norway; and University Hospital in Florence, Italy. These centers all use the ENIGI Mental Health protocol. The first trans persons were included in the ENIGI Endocrine protocol in 2010. Data presented in this article represent an update of our inclusions until March 12, 2015. At that time the first conference of the European Professional Association for Transgender Health (EPATH) was organized in Ghent, Belgium. Inclusion of trans persons is still ongoing in all participating centers.

The overall study protocol was approved by the Ethical Committee of Ghent University Hospital, Belgium. Every participating clinical center also obtained approval of their local ethical committees.

Study Participants

All patients underwent a standardized diagnostic procedure to confirm the diagnosis GD/gender incongruence and assess eligibility for treatment. The procedure of the ENIGI Mental Health protocol is described in Kreukels et al.[4] In short, the mean duration of the diagnostic phase varies between 6 and 12 months and consists of regular meetings with a psychologist and/or a psychiatrist. Once the diagnosis has been confirmed and there are no physical, psychological or social contraindications, hormonal treatment is started. In all centers, psychological counselling is offered during this phase, which is also called the "Social Transition Phase." During this 12- to 18-month period, persons experience life in the desired gender role on a daily basis. Once persons successfully go through this phase and there are no somatic contraindications, they are referred to the surgeon if they desire gender affirming surgery. All included subjects are above 16 years (Ghent and Oslo), above 17 years (Amsterdam), or above 18 years (Florence).

People are included in the ENIGI Endocrine protocol when they start medical treatment for GD/gender incongruence. Data on fulfillment of diagnostic criteria of current manuals for classification is collected in the ENIGI Mental Health protocol. Patients are eligible to participate if they have not used cross-sex hormones before and if they have sufficient knowledge of the native languages: Dutch or French for participants from Ghent, and Dutch, Italian, and Norwegian for patients from Amsterdam, Florence, and Oslo, respectively. At the start of CHT, patients receive oral and written information of the ENIGI endocrine protocol by their physician and written informed consent is obtained according to the institutional guidelines.

Treatment Protocol

Trans women

Cyproterone acetate in a once daily dose of 50 mg is started in combination with an estradiol agent. In Ghent, Amsterdam, and Florence, estradiol valerate is prescribed 2 mg twice daily, whereas in Oslo 4 mg is given in 1 single dose. Although not well established, the ENIGI medical team felt that risk of thrombosis from estrogens was greater with oral agents than with transdermal preparations, perhaps due to the "first pass effect" of the liver. Therefore the protocol calls for transdermal estrogens for patients older than 45 years of age. In Amsterdam and Ghent we prescribe estradiol patches in a dose of 100 mcg/24 hours. For some medical conditions, such as a history of thrombosis, treatment is started at a lower dose. In Florence patients can also choose from estradiol emidrate gel 1 mg twice daily.

Trans men

As not all testosterone treatment regimens are reimbursed in the different European countries, treatment protocols differ between the clinical centers. In Ghent and Oslo, testosterone undecanoate 1000 mg once per 12 weeks (Nebido) is prescribed. In the Netherlands, currently testosterone undecanoate injections are not covered by health insurance companies, so most patients choose between testosterone gel in a daily dose of 50 mg or testosterone esters 250 mg injections (Sustanon) every 2