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Increased psychiatric morbidity in women with complete androgen insensitivity syndrome or complete gonadal dysgenesis

Hedvig Engberg[a,b,*], Anna Strandqvist[c,d,e], Anna Nordenström[c,d], Agnieszka Butwicka[f,g], Agneta Nordenskjöld[h,i,j], Angelica Lindén Hirschberg[d,k], Louise Frisén[a,b]

[a] Department of Clinical Neuroscience, Karolinska Institutet, SE-171 77 Stockholm, Sweden
[b] Child and Adolescent Psychiatry Research Center, Gävlegatan 22B, SE-113 30 Stockholm, Sweden
[c] Department of Pediatric Endocrinology, Astrid Lindgren Children's Hospital, Karolinska University Hospital, SE-171 76 Stockholm, Sweden
[d] Department of Women's and Children's Health, Karolinska Institutet, SE-171 77 Stockholm, Sweden
[e] Department of Psychology, Karolinska University Hospital, SE-171 76 Stockholm, Sweden
[f] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE-171 77 Stockholm, Sweden
[g] Department of Child Psychiatry, Medical University of Warsaw, Żwirki i Wigury 61, PL-02-091 Warsaw, Poland
[h] Department of Molecular Medicine and Surgery, Karolinska Institutet, SE-171 77 Stockholm, Sweden
[i] Center for Molecular Medicine, Karolinska Institutet, SE-171 77 Stockholm, Sweden
[j] Pediatric Surgery, Astrid Lindgren Children's Hospital, Karolinska University Hospital, SE-171 76 Stockholm, Sweden
[k] Department of Gynecology and Reproductive Medicine, Karolinska University Hospital, SE-171 76 Stockholm, Sweden

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ABSTRACT

Objective: Knowledge concerning mental health outcomes is important to optimize the health of individuals with disorders or differences of sex development (DSD). Thus, the aim of this study was to estimate if the prevalence of psychiatric morbidity in adult women diagnosed with complete androgen insensitivity syndrome (CAIS) or complete gonadal dysgenesis (46,XY GD and 46,XX GD) differs from that in women with premature ovarian insufficiency (POI) or age-matched population controls.

Methods: This cross-sectional study was conducted at the Karolinska University Hospital, Stockholm, Sweden, and included 33 women with different DSDs: 20 CAIS, 6 46,XY GD, 7 46,XX GD, 21 women with POI and 61 population-derived controls. Psychiatric morbidity was assessed using the Mini International Neuropsychiatric Interview plus (MINI +). To complement the MINI +, three self-report questions were used to evaluate current and previous psychiatric history. Results are presented as *p* values and estimated risks (odds ratio [OR], 95% confidence intervals [CI]) of psychiatric conditions among women with CAIS or GD in comparison with women with POI and age-matched population-derived controls.

Results: Twenty-eight of the 33 women (85%) with CAIS or GD met the criteria for at least one psychiatric disorder according to the MINI +, with depression and anxiety disorders being most common. This was significantly higher compared with population controls (52%) (OR 5.1, 95% CI 1.7–14.9), but not compared to women with POI, who had a high frequency of psychiatric diagnoses (76%).

Conclusion: The increased psychiatric morbidity in women with CAIS and GD highlights the need for clinical awareness of the psychiatric vulnerability in these patients.

1. Introduction

Disorders or differences of sex development (DSD) include rare congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical [23]. There are women with DSD who remain undiagnosed until adolescence when they seek medical attention because of primary amenorrhea and an absence of secondary sex characteristics. Women with complete androgen insensitivity syndrome (CAIS) have a 46,XY karyotype and intra-abdominal testes. Due to a mutation in the androgen receptor gene their bodies are unable to respond to circulating testosterone. Externally, they have a complete female phenotype, but no female internal reproductive organs (i.e.,

* Corresponding author at: Department of Clinical Neuroscience, Center for Psychiatric Research, Child and Adolescent Psychiatry Research Center, Gävlegatan 22B, SE-113 30 Stockholm, Sweden.
E-mail addresses: hedvig.engberg@ki.se (H. Engberg), anna.strandqvist@ki.se (A. Strandqvist), anna.nordenstrom@ki.se (A. Nordenström), agnieszka.butwicka@ki.se (A. Butwicka), agneta.nordenskjold@ki.se (A. Nordenskjöld), angelica.hirschberg.linden@ki.se (A.L. Hirschberg), louise.frisen@ki.se (L. Frisén).

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uterus, ovaries) and therefore cannot carry a pregnancy. To date, there are no known cases of individuals with CAIS conceiving biological children since the testes do not produce sperm, albeit germ cells have been detected in younger individuals [5,16]. Complete gonadal dysgenesis (GD) can imply a 46,XX, as well as, a 46,XY karyotype [15]. Both 46,XX and 46,XY GD are characterized by a lack of typical gonadal development and sex hormones; however, a uterus develops because of the absence of anti-müllerian hormone. CAIS and GD occur in approximately 5 and 1 per 100,000 individuals, respectively [22,27].

Psychological well-being and mental health are important aspects of the quality of life (QoL) and, according to the DSD consensus statement, psychosocial care should be an integral part of the management to promote positive adaptation [23]. Outcome studies have focused on aspects of psychosexual development, especially gender dysphoria [8,39] and sexual functioning [14,17]. Previous studies have shown that the perceived QoL is good, but having a DSD diagnosis is, nevertheless, associated with psychological distress [10,32,41]. In addition, psychiatric morbidity has been studied, but self-report instruments and a lack of control groups hampers the interpretation of the results [47].

DSD conditions are often used as so-called “model disorders” for hyperandrogenism (e.g., congenital adrenal hyperplasia [CAH]) [21] or hypoandrogenism (e.g., CAIS, 46,XY GD) because of the hypothesis that prenatal androgens exert organizational effects on brain structure and function. Androgens are known to influence many gender-related behaviors [18,21,33] and have also been hypothesized to influence psychiatric morbidity, although the reported results are inconclusive [6]. A lack of ovarian steroid synthesis is known to have serious consequences for women's health [36].

Women with CAIS or GD lack the organizing effects of sex hormones during fetal life. This is in contrast to the acquired lack of sex hormones in women with premature ovarian insufficiency (POI), defined by secondary amenorrhea and hypergonadotropic hypogonadism before the age of 40 years [46]. Women with POI have a typical female hormonal situation from fetal life through puberty and into adulthood. The prevalence of POI is approximately 1% [46] and, together with women with CAIS and GD, they might face similar challenges regarding fertility and other aspects of being a woman [28,48]. We hypothesized that a lack of sex hormones and organizational effects during fetal life would increase the frequency of psychiatric morbidity in women with CAIS and GD and that this would differ from that of women with an acquired hormonal deficiency like POI and of age-matched population-derived controls. The aim of this study was therefore to investigate the prevalence of psychiatric morbidity in women with a prenatal deficiency of sex hormone effects, i.e., CAIS and GD, compared to those with an acquired hormone deficiency in adulthood, i.e., POI, and compared to controls with a typical female hormonal situation.

2. Material and methods

2.1. Setting

This is part of a cross-sectional follow-up study of a cohort of patients at the Karolinska University Hospital in Stockholm, Sweden. To take part in the whole study, active participation on site during one or two days was required. Patients and controls were recruited from September 2011 until June 2016. Inclusion criteria were female sex, 18 years of age or older at the time of assessment and ability to speak and/or understand Swedish. All participants gave their written informed consent to participate and were informed that they could withdraw from the study at any time. Ethical approval was obtained from the Regional Ethics Committee.

2.2. Study population

2.2.1. Women with CAIS and GD

The recruitment of participants was accomplished by contacting the different DSD teams in Sweden. As of September 2011, all Swedish women with CAIS (n = 21) or GD (n = 15) known to us and a confirmed genetic diagnosis, and therefore eligible for the study, were contacted, mainly from the Department of Obstetrics and Gynecology, Karolinska University Hospital, as part of a multidisciplinary study focusing on somatic and psychiatric outcomes in women with DSD. Thirty-five of the 36 women who were asked to participate were finally included, and 33 of the 35 (94%) participated in the MINI + structured diagnostic interview. One individual with CAIS declined all participation in the study.

2.2.2. Women with POI

46,XX women with POI (n = 21) were recruited for the study via the Department of Obstetrics and Gynecology, Karolinska University Hospital. Only women with primary POI, not secondary to oncological treatment, were recruited. All women with POI who were asked to participate were finally included, and they all participated in the MINI + structured diagnostic interview.

2.2.3. Population-derived controls

The following procedure was used when sampling controls: Letters were sent out to women living in the greater Stockholm area who matched study participants by year and date of birth. Reminders to non-responders were not sent but, instead, the next person in the general population registry was invited. In total, 669 invitational letters were sent out with the aim of having at least one matched control per patient, and 61 controls were recruited in the end.

2.3. Clinical interview and assessments

The Mini International Neuropsychiatric Interview plus (MINI +) is a structured diagnostic interview that permits diagnosis of 23 DSM-IV Axis 1 psychiatric diseases experienced at any time in life, including the specific time of the study response [42]. It is the most widely used psychiatric structured diagnostic interview instrument and has high sensitivity (0.70–0.94) and specificity (0.72–0.97). The same psychiatrically trained physician performed the majority of the MINI + interviews with both patients and controls. However, due to scheduling difficulties, some interviews were performed by a clinical psychologist or by another psychiatrically trained physician. If the participant met the criteria for a psychiatric disease at that time, the participant was informed and, if so desired, was referred to specialist care. The interviews lasted 15–60 min. The interviewers were not blinded to the purpose of the study, but they were not aware of the exact diagnoses of the women – only if they were controls or not. The MINI assesses present psychiatric status and lifetime prevalence, but it does not assess whether the individual has sought previous healthcare attention for psychiatric problems. It also does not investigate the present or past use of psychotropic drugs. Therefore, three questions assessing these issues were added: Have you ever been in contact with healthcare services because of mental health problems? Are you taking any medication (psychotropic drugs) at the moment? Have you ever taken any medication for mental health problems?

2.4. Statistical analyses

The statistical analysis was carried out using IBM SPSS Statistics 22. The χ^2 test or Fisher's exact test was used for categorical data to assess differences in the frequency of psychiatric disorders across groups. Significant variables were included in a logistic regression model to estimate risks (odds ratios, ORs) for the significant differences. ORs with a 95% confidence interval not including 1 and $p < 0.05$ were considered significant. Subgroup analyses were performed for women with CAIS. Women with 46,XX GD and 46,XY GD were excluded from subgroup analyses due to low statistical power.