



Congenital adrenal hyperplasia and risk for psychiatric disorders in girls and women born between 1915 and 2010: A total population study



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ABSTRACT

Congenital adrenal hyperplasia (CAH) is a chronic condition and individuals are exposed to elevated androgen levels *in utero* as a result of the endogenous cortisol deficiency. Prenatal androgen exposure has been suggested to influence mental health, but population based studies on psychiatric morbidity among girls and women with CAH are lacking.

Therefore, we performed a cohort study based on Swedish nationwide registers linked with the national CAH register. Girls and women with CAH due to 21-hydroxylase deficiency ($n = 335$) born between January 1915 and January 2010 were compared with aged-matched female ($n = 33500$) and male controls ($n = 33500$). Analyses were stratified by phenotype [salt wasting (SW), simple virilizing (SV), and non-classical type (NC)] and by *CYP21A2* genotype subgroups (null, I2splice, I172N, and P30L). Results are presented as estimated risks (OR, 95%CI) of psychiatric disorders among girls and women with CAH compared with age-matched controls.

Any psychiatric diagnoses were more common in CAH females compared with female and male population controls [1.9 (1.4–2.5), and 2.2 (1.7–2.9)]. In particular, the risk of alcohol misuse was increased compared with female and male population controls [2.8 (1.7–4.7) and 2.1 (1.2–3.5)], and appeared most common among the girls and women with the most severe null genotype [6.7 (2.6–17.8)]. The risk of stress and adjustment disorders was doubled compared with female population controls [2.1 (1.3–3.6)].

Girls and women with CAH have an increased risk of psychiatric disorders in general and substance use disorders in particular compared with unexposed females, with the highest risk among those with the most severe genotype. Prenatal androgen exposure and deficient endogenous cortisol and/or adrenaline production may provide explanations for these findings, but other factors related to CAH cannot be excluded.

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1. Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder with an incidence ranging from 1/10000 to 1/15000 live births (Merke and Bornstein, 2005). The most common form (95%) of CAH is caused by mutations in the *CYP21A2* gene encoding 21-hydroxylase, resulting in deficient cortisol and mineralocorticoid production and a concomitant accumulation of steroid precursors that are converted into adrenal androgens. If left untreated, the condition is lethal in severe cases due to salt crisis. However, mortality is slightly increased even in glucocorticoid treated CAH patients mainly due to the adrenal crisis during severe infections (Falhammar et al., 2014b). The glucocorticoid and mineralocorticoid substitution aims to replace the cortisol insufficiency, prevent salt crisis, and to decrease the ACTH production, thereby normalizing the androgen levels. However, oral glucocorticoids cannot completely mimic the normal circadian rhythm of cortisol and most patients are over-treated leading to an increased risk of long-term complications such as the metabolic syndrome and osteoporosis (Falhammar and Thorén, 2012). Classic forms of CAH result in exposure to elevated androgen levels *in utero* and 46,XX infants are born with varying degrees of virilization of the external genitalia. CAH has therefore been conceptualized as a model to elucidate organizational effects of prenatal androgen exposure (Ehrhardt et al., 1968). 46,XX children with CAH are typically raised as girls and may be subjected to feminizing genital surgery.

Clinical features, including the degree of virilization, are strongly associated with the *CYP21A2* genotype (Wedell, 2011). The classic phenotypes of CAH are the salt wasting (SW) and the simple virilizing (SV) forms. The SW phenotype is associated with null mutations that completely abolish enzyme activity, and with the slightly less severe I2 splice mutation. The SV phenotype associated with the I172N mutation result in a less severe phenotype in which patients are less prone to salt loss. Finally, patients with the non-classic (NC) form typically present later in life due to symptoms of androgen excess such as growth acceleration, hirsutism, or infertility. The NC form of CAH is most frequently associated with the V281L mutation in the Swedish cohort.

Psychosexual development has been extensively studied in women with CAH (Berenbaum et al., 2000, 2004; Frisén et al., 2009; Jaaskelainen and Voutilainen, 2000; Johannsen et al., 2006a; Kuhnle et al., 1995; Meyer-Bahlburg et al., 2004; Nordenström et al., 2010; Slijper et al., 1998). Quality of life has also been studied in CAH, though with conflicting results where outcomes range from positive (Berenbaum et al., 2004; Reisch et al., 2011) to negative (Art et al., 2010; Neramo et al., 2010). Much less is known about psychiatric morbidity among these patients. Some previous studies have reported increased rates of psychiatric symptoms among children, adolescents, and adult women with CAH (Liang et al., 2008; Meyer Bahlburg et al., 2008; Mueller et al., 2010), whereas another study did not show increased rates of psychiatric disorders compared to norm data (Morgan et al., 2005). We recently reported that men with CAH have an increased rate of psychiatric disorders, suicides or suicide attempts, and substance misuse (Falhammar et al., 2014a).

The primary purpose of this study was to estimate the frequency of psychiatric disorders in a large unbiased cohort of girls and women with CAH due to 21-hydroxylase deficiency. Moreover, we wanted to assess if the outcomes varied between the different pheno- and geno-type groups and between individuals born before or after the introduction of nationwide neonatal screening in 1986. We analyzed our results in comparison with age-matched female and male population-based controls and stratified our results based on whether the diagnosis was made before or after 18 years of age.

2. Material and methods

2.1. National registers

A cohort study based on Swedish nation-wide registers was conducted. In Sweden, a unique national registration number is assigned to each resident at birth or, for resident immigrants, upon arrival to the country. This number is used in all official records and provides an opportunity to link data from population-based registers. This study used data from the National Register of CAH (Gidlöf et al., 2013; Strandqvist et al., 2014), the National Patient Register (NPR) (Ludvigsson et al., 2011), the Cause of Death Register (held by the National Board of Health and Welfare), and the Total Population Register. The National Register of CAH comprised data on 612 patients (Gidlöf et al., 2013). Among them, 606 individuals had a clinically or genetically confirmed 21-hydroxylase deficiency. NPR contains discharge diagnoses for all psychiatric inpatient episodes since 1973 and diagnoses from psychiatric outpatient care since 2001 (Ludvigsson et al., 2011). All data were analyzed anonymously.

2.2. Exposed subjects

Girls and women with a CAH diagnosis and a confirmed 21-hydroxylase deficiency born from January 1915 to January 2010 were identified in the National CAH register ($n = 306$) (Gidlöf et al., 2013; Strandqvist et al., 2014). An additional 29 patients were included who had received a CAH diagnosis (ICD-8 codes 255.01, 255.08; ICD-9 codes 2552, 255C; and ICD-10 code E25.0) more than twice in NPR, and not subsequently been diagnosed with Addison's disease, Cushing's syndrome, acromegaly, or had received treatment with glucocorticoids due to malignancies (Strandqvist et al., 2014). Patients for whom the *CYP21A2* genotype was known were categorized into the most prevalent genotype groups based on the allele associated with the mildest mutation: null, I2splice, I172N, P30L, to V281L (ranging from most severe to mildest) (Gidlöf et al., 2013; Strandqvist et al., 2014). Patients with unknown *CYP21A2* mutations were categorized according to clinical severity of CAH when sufficient clinical data were available (Gidlöf et al., 2013). The median age of the sample was 25.3 with 53% of the cohort born 1985 or earlier (Table 1). Neonatal screening for CAH was introduced in Sweden 1986. The young median age is explained by the large differences in the survival rate during different time periods with low number of surviving individuals during the earlier years (Gidlöf et al., 2013). The data was also stratified based (i) on whether the diagnosis was made before or after 18 years of age, (ii) based on whether subjects were born before or after the introduction of neonatal screening in 1986, (iii) by the age groups <12.0 years, 12.0–17.9 years, and ≥ 18.0 years, and (iv) controlled for parents' higher education.

2.3. Unexposed subjects

For each individual with CAH, 100 girls and women and 100 boys and men matched for birth year and county of birth were randomly selected from the Total Population Register. Patients who had immigrated to Sweden were matched for this factor as well. In total, 33500 unexposed females and 33500 unexposed males were identified and used as controls.

2.4. Psychiatric diagnoses

Information on psychiatric diagnoses was drawn from NPR using the International Classification of Diseases (ICD) codes. Data on completed suicides were extracted from the Cause of Death Register. Primary outcome measures were: (1) suicidal

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