REVIEW

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Psychosocial Development, Sexuality and Quality of Life in Congenital Adrenal Hyperplasia

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Abstract

Exposure of the developing brain to androgens during fetal life is known to affect sexual development, including postnatal sex and sexual orientation. However, these relationships are both multifactorial and unpredictable. It is generally assumed that congenital adrenal hyperplasia (CAH) has greater effects in women than in men due to non-physiological adrenal androgen excess. Outcome information on patients with CAH often indicates poor quality of life, general maladjustment, problems with sexuality, and decreased fertility. With advances in medical treatment and surgery and changes in societal perspectives on gender and sexuality, there is a need for greater consideration of quality of life factors, including socialization and sexuality.

Keywords: Congenital adrenal hyperplasia, sexuality, quality of life, psychosocial development

Introduction

In disorders of sex development, compatibility between psychosexual identity and assigned gender is important. Sexuality in congenital adrenal hyperplasia (CAH) should be evaluated by taking into account the patient's karyotype and the gender being raised. The frequency of disorders in psychosocial and cognitive domains in patients with CAH is higher than in the normal population, and these disorders are related to the high prenatal androgen load, the patient's karyotype, and supraphysiological glucocorticoid treatment in the postnatal period.

Evaluating the quality of life in children with CAH and identifying and improving the factors affecting it are of critical importance for making the lives of these children and their families easier. A multidisciplinary approach that provides good clinical control and appropriate surgical management positively affects the quality of life.

This review was developed by the 'Adrenal Study Subgroup' of the 'Pediatric Endocrinology and Diabetes Association of Turkey'. We have prepared a review of Psychosocial Development, Sexuality and Quality of Life in Congenital Adrenal Hyperplasia in childhood and adolescence. The overall aim of this evidence-based review is to provide good practice points with a focus on recommendations for daily management.

Psychosexual Development in Congenital Adrenal Hyperplasia

Gender Identity and Sexual Health

46,XY male patients: It is reported that patients reared as males in parallel with karyotype do not have gender identity disorder and their frequencies of marriage or sexual intercourse are similar to those of healthy individuals. Gender dysphoria has not been reported (1,2). In a case-controlled study including males with CAH and healthy

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European counterparts, sexual health in males with CAH was shown to be comparable to those of healthy controls, and sexual problems in these patients were attributed to psychosocial problems, such as anxiety and depression (3).

46,XX female patients: Although virilized females tend to have more interest in games for males than age-matched healthy counterparts, gender dysphoria has not been reported (4,5,6,7). The preference for male toys in 46,XX females with CAH has been associated with parental guidance (8). Increased androgen excess in the perinatal period is not associated with sexual orientation in the postnatal period. However, homosexual or bisexual orientation has rarely been observed in 46,XX virilized females in the postpubertal period. A recent review suggested a greater tendency for gender identities in 46,XX females with CAH other than heterosexuality compared to the normal population (9).

A case series study investigating the impact of the diagnosis of CAH on sexuality has suggested lack of sufficient knowledge in young adult patients with CAH and differences among the patients in perception of the impact of the disease on sexuality (10).

46,XX females with classical CAH have been reported to spend more time with their female peers and have a higher frequency of male-specific activities than their non-classical CAH counterparts (11,12).

46,XX patients raised as males: Although an increased frequency of gender identity disorder has been noted in 46,XX patients raised as males, gender dysphoria is not encountered in the presence of adequate social support. It has been suggested that caution should be practiced in assessment of the studies that drew data mostly from non-validated interviews (9).

Cognitive and Neurological Functions in Patients with Congenital Adrenal Hyperplasia

Prenatal androgen overload, prenatal use of dexamethasone and the dose of the glucocorticoid treatment are significant factors associated with adverse impact on the neuropsychiatric development of patients with CAH (1). The hypothalamohypophyseal axis and sex hormones interact with the hypothalamus, amygdala and hippocampus. Intellectual impairment has been shown to be associated with endogeneous hormonal imbalance, nonphysiological glucocorticoid replacement and subclinical cerebral ischemia owing to differentiation of oligodendroglia (13).

Prenatal dexamethasone has been reported to lead to improvement in cognitive functions in girls with CAH. However, prenatal dexamethasone may have detrimental effects on the cognitive functions of healthy girls (14).

Females with CAH have been reported to have better spatial targeting performance than healthy controls but similar capacities of mental rotation when compared to healthy counterparts. Mental rotation capacity is disturbed in 46,XY male patients with CAH while the targeting capacity is intact. A recent meta-analysis reported spatial cognition to be comparable to healthy controls in 46,XX girls with CAH (15) whereas in 46,XY male patients it was shown to be compromised (15). Gender related differences in spatial capacities have been associated with mini-puberty or different social factors (15).

Studies on learning difficulties in patients with CAH are scanty (16,17,18). Salt-wasting patients with CAH are reported to have learning difficulties more frequently than simple virilizing counterparts (17,18), although a study with contradictory results does exist (16).

46,XX females with CAH have lower verbal and performance IQ values than healthy controls. In addition, salt-wasting patients have lower total and verbal IQ values than simple virilizing females (19). Attention deficit and hyperactivity disorder is reported to be more frequent in patients with CAH than in healthy controls (20). The frequencies of psychiatric problems and substance abuse are higher than the general population in 46,XX females with CAH (21).

Fertility

In 46,XX female patients with CAH, fertility is reduced and this reduction is more pronounced in salt-wasting forms of CAH. The reasons for reduced fertility in these patients may be: delayed psychosexual development; decreased sexual activity; reluctance for marriage; negative impact of alterations in stature on sexual functions; menstrual irregularity and anovulation; polycystic ovary syndrome; disturbance in the clitoral neural network; morphological changes owing to genital surgery; and vaginal stenosis (1). When patients with classical CAH and those with non-classical CAH were compared with healthy controls in terms of sexual dysfunction and associated anxiety, patients in the latter group were found to be more disadvantaged than the others, which is most likely due to delayed diagnosis in non-classical CAH patients (22). In 46,XX female patients with CAH, the fear of stigmatization was reported to have an adverse impact on romantic relationships (23).

In 46,XX female patients with CAH, a relative reduction in offspring number was reported. However, successful spontaneous pregnancies occur following corrective surgery in severely virilized patients with CAH (24).

In patients with late onset CAH, hyperandrogenism and related menstrual problems are more frequent than healthy

controls, and the total number of pregnancies and birth rates are lower (25).

46,XY male patients with classical CAH are reported to have reduced fertility, and this is associated with the presence of testicular adrenal rest tumors (TARTs) (26). These benign tumors compress the seminiferous tubules leading to testicular atrophy and reduction in sperm counts. Increased adrenal androgens may also lead to infertility via suppression of the hypothalamo-hypophyseal-gonadal axis (27).

In conclusion, patients with CAH should be regularly followed in a multi-disciplinary center with state-of-the art care in endocrinology, psychological assessments and surgery. Sexuality in CAH should be assessed considering the karyotype of the patient and gender of rearing. The frequencies of disturbances in psychosocial and cognitive areas in patients with CAH are higher than those in the normal population, and these disturbances are related to excess prenatal androgen overload, the karyotype of the patient and supraphysiological glucocorticoid treatment in the postnatal period. There is a call for consensus in psychosocial evaluation of patients with CAH.

Good practice points:

1. In patients with CAH due to 21-hydroxylase deficiency, sexuality should be evaluated in accordance with the peripheral blood karyotype and gender of rearing (2⊕⊕OO).

2. The frequencies of psychosocial and cognitive disturbances in patients with CAH are higher than those in healthy controls owing to prenatal androgen excess, postnatal supraphysiological glucocorticoid treatment and the karyotype of the patient (2⊕⊕OO).

3. Fertility is reduced in patients with CAH, and it is associated with the disease phenotype (2⊕⊕OO).

Quality of Life in Patients with Classical Congenital Adrenal Hyperplasia

Quality of life is defined as an individual's perception of his/her position in life in relation to his/her goals, expectations, standards, and concerns in the context of the culture and value systems in which he/she lives. It is a broad concept that is affected in a complex fashion by a person's physical health, psychological state, level of independence, social relationships, and relationships with salient features of his/her environment (28). Health-related quality of life refers to "the patient's sense of health and well-being in broad areas of physical, psychological, and social functioning" (28). In recent years, advances in medical treatment of chronic diseases leading to increased survival rates have shifted the focus to quality of life of affected patients (29).

In patients with classical CAH, problems that become prominent in different age groups can affect the quality of life of patients (30,31,32). These start from the moment of diagnosis, and include factors such as the need for lifelong treatment, treatment compliance, operations performed due to ambiguous genitalia and their outcomes, complications related to the disease or treatment (short stature, obesity, osteoporosis, TARTs), problems related to sexual life, and fertility concerns. While many studies investigating quality of life in adults with CAH, particularly women, have focused on exploring the impact of high androgen exposure during brain development, only a few studies have been conducted to examine quality of life in children with CAH (20,33,34,35). Since there is no health-related quality of life scale specifically designed and validated for children with CAH, validated health-related quality of life scales that assess pediatric chronic diseases have been used (36,37,38).

Numerous studies have shown that health-related quality of life may be adversely affected in children with CAH compared to the general population (30,33,39). It has been reported that there is a general decrease in quality of life in children and adolescents with CAH, with psychological and social domains showing lower scores than physical and environmental domains (39,40). Similar studies have reported increased rates of psychiatric symptoms in children and adolescents with CAH (21,33,41,44).

Children with CAH have impaired physical, emotional, social, and school functioning compared to the general pediatric population (33). Parents of children with CAH perceive their children as more vulnerable than their peers. Considering the specific areas of parent reports, lower scores were found in the emotional domain (consisting of questions covering feelings of fear, sadness, anger, and fear about the future) and the school domain (absenteeism problems and keeping up with school work) (33). However, in a study from the Netherlands, although the disease had a slightly negative impact on the physical, social, and community functioning of children with CAH, their quality of life did not decrease. These children experienced several daily health-related problems that did not interfere with their daily activities and participation in society (34).

Older children and adolescents have lower quality of life scores in psychological and social domains, in addition to lower total scores (39). Adolescent patients are more concerned about their health, more fearful of lifelong complications of their chronic diseases, and more uncomfortable with long-term medications. Meanwhile,

since it may be related to high ACTH exposure, cases with higher Prader scores and higher virilization reported lower scores in the physical domain and total scores (39).

Recent studies have demonstrated a decrease in quality of life in CAH patients, who tend to be single and less sexually active, exhibit less self-confidence, are less sociable and feel less social acceptance, and have a negative body image (45,46).

Considering the difference between sexes, the quality of life in females with CAH is lower than in males. Operations due to ambiguous genitalia and their outcomes, body structure, difficulties in sexual life, fertility problems, and psychosocial problems are more common in females and adversely affect the quality of life (21,39,40,43). However, there are also studies reporting no difference between sexes in terms of health-related quality of life (32,33).

Women who underwent clitoroplasty scored higher in the psychological domain than those who did not have surgery. After feminizing genitoplasty, women were shown to have a better quality of life and mental health since they have fewer distressing symptoms (39). Furthermore, there may be poor quality of life and psychiatric symptoms due to too late genital intervention, poor surgical outcomes, or distressing memories (19,47). There is a correlation between the timing of surgery and quality of life. Whereas patients who undergo clitoroplasty at an older age have lower quality of life scores in the psychological domain, it has been shown that early surgery and early creation of an external genital appearance appropriate to the genetic sex contribute to reducing the anxiety of parents and children and lead to better psychosocial adjustment (48,49). However, in contrast to these studies, some studies do not show a correlation between behavioral outcomes or psychological adjustment and age at genitoplasty in women with CAH. It has been reported that genital surgery in childhood frequently leads to feelings of loss of body ownership and resentment (50,51). In general, the current evidence supports early feminizing genitoplasty (39).

Studies have shown that childhood adrenal crisis has a significant impact on health-related quality of life (30,52). Patients who are compliant with treatment receive higher scores in social and environmental domains and total scores than those who are non-compliant. Easy access to medical services and regular follow-ups are known to lead to better health-related quality of life. Furthermore, regular follow-ups and good compliance with treatment lead to fewer complications, better CAH control, and, therefore, higher quality of life (39). On the contrary, it has been reported that CAH patients who develop chronic diseases, such as hypertension, score lower in physical and social relationships and environmental domains (42). Of note, health-related quality of life scores of patients with salt-wasting CAH were found to be lower than those with simple virilizing types (20,32,39).

No correlation was found between quality of life and hydrocortisone dose (33,39). Moreover, patients receiving high doses of mineralocorticoids have lower quality of life scores in the psychological domain. It was shown that patients with high serum Δ4 androstenedione levels score lower in psychological and social domains. No significant relationship was detected between serum 17-hydroxyprogesterone and testosterone levels and quality of life, except for the physical domain (39,44,50).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (53).

Good practice points:

1. CAH patients and their families should be supported in terms of the physical and psychosocial problems they experience in childhood and adolescence before patients reach adulthood (1⊕⊕⊕O).

2. The currently available evidence suggests early feminizing genitoplasty to improve quality of life (2⊕⊕OO).

3. Good compliance with treatment is a factor that increases the quality of life, and cases should be followed up closely and regularly (ungraded good practice point).

Footnotes

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Authorship Contributions

Concept: Ahmet Uçar, Eda Mengen, Zehra Aycan, Design: Ahmet Uçar, Eda Mengen, Zehra Aycan, Data Collection or Processing: Ahmet Uçar, Eda Mengen, Zehra Aycan, Analysis or Interpretation: Ahmet Uçar, Eda Mengen, Zehra Aycan, Literature Search: Ahmet Uçar, Eda Mengen, Zehra Aycan, Writing: Ahmet Uçar, Eda Mengen, Zehra Aycan.

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