Gender Role Behavior, Sexuality, and Psychosocial Adaptation in Women with Congenital Adrenal Hyperplasia due to *CYP21A2* Deficiency

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Context: Gender-atypical behavior has been described in young girls as well as in women with congenital adrenal hyperplasia (CAH) due to a *CYP21A2* deficiency.

Objective: The aim of the study was to assess health-related, psychosexual, and psychosocial parameters and correlate the results to *CYP21A2* genotype.

Design and Participants: Sixty-two Swedish women with CAH and age-matched controls completed a 120-item questionnaire and a validated quality of life instrument [psychological general well-being (PGWB) formula] to identify psychosexual and psychosocial parameters. The patients were divided into four *CYP21A2* genotype groups.

Results: The women with CAH held more male-dominant occupations (30%) compared to controls (13%) ($P = 0.04$), especially those in the null genotype group (55%) ($P = 0.006$). They also reported a greater interest in rough sports (74%) compared to controls (50%) ($P = 0.007$). Eight women with CAH (14%) reported a prime interest in motor vehicles, compared to none of the controls ($P = 0.002$). Non-heterosexual orientation was reported by 19% of women with CAH ($P = 0.005$), 50% in the null genotype group ($P = 0.0001$), 30% in I2splice (NS), and 5% in I172N (NS). PGWB total score did not differ between patients and controls.

Conclusion: We identified increased gender-atypical behavior in women with CAH that could be correlated to the *CYP21A2* genotype. This speaks in favor of dose-dependent effects of prenatal androgens on the development of higher brain functions. The impact of the disease on upbringing and interpersonal relationships did not correlate with disease severity, indicating that other factors, such as coping strategies, are important for psychosocial adaptation. This illustrates the need for psychological support to parents and patients. **(*J Clin Endocrinol Metab* 94: 3432–3439, 2009)**

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder, caused in most cases (95%) by mutations in the *CYP21A2* gene encoding 21-hydroxylase. The enzyme deficiency results in a lack of cortisol and aldosterone as well as increased levels of androgens. The increased androgen levels during early embryonic development lead to varying degrees of virilization of external genitalia in females, which may result in uncertainty of sex assignment at birth. Surgical correction of genitalia, if necessary, is usually performed during the first year of life. Pharmacological treatment consists of glucocorticoid and, in many cases, mineralocorticoid substitution.

The molecular genetics in *CYP21A2* deficiency have been extensively characterized. There is a strong correlation between genotype and clinical presentation (1). Patients with mutations that completely abolish the enzyme activity, referred to as null mutations, have the most severe form of the disease. The I2splice mutation is slightly less severe. These two mutations represent the salt-wasting (SW) form that, if untreated, leads to life-threatening salt

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Abbreviations: CAH, Congenital adrenal hyperplasia; NC, nonclassical; NS, not significant; PGWB, psychological general well-being; QoL, quality of life; SV, simple virilizing; SW, salt-wasting.

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crises in the neonatal period. The I172N mutation is associated with the simple virilizing (SV) variant, in which the patients are spared salt loss. Girls with the SW and SV forms are born with severely virilized external genitalia, although this is often less pronounced among SV than SW patients. The nonclassical (NC) form of CAH, frequently associated with V281L mutation, does not cause prenatal virilization and may escape clinical identification until later in childhood or in adult life when the patient may seek medical attention due to symptoms of androgen excess.

Androgens have been suggested to exert an organizational effect on higher brain function during fetal development and an activating effect during puberty (2). Studies of gender-related traits in CAH have been used to demonstrate the organizational effects of prenatal androgen exposure on the developing brain. In 1968, it was first shown that girls with CAH have a masculinized behavior (3). Since then, this has been repeatedly reported, *e.g.* regarding childhood play behavior, aggressive behavior, and spatial perception (4–10). Recalled childhood behavior correlates with adult gender-related behavior, such as sexual orientation and choice of profession, as well as leisure activities (11–14). Prenatal androgens are believed to have a dose-dependent rather than a threshold effect (12, 15). The determinants of gender identity are, however, much less known. Gender identity is not in a convincing manner related to prenatal androgen exposure (11, 12). For example, masculinization of core gender identity is not associated with prenatal androgenization, as estimated by the severity of genital virilization (16, 17). Most women with CAH are heterosexual, but an increased prevalence of homosexual and bisexual orientation has been reported, with frequencies ranging from 3 to 31% (7, 12, 15, 18). Impaired sexual function has been identified in women with CAH (19–21). The literature on other quality of life (QoL) factors is less consistent, although many authors emphasize the good psychological adjustment (20, 22–24). In contrast, impaired QoL and increased psychiatric morbidity were found in two recent publications (25, 26).

We have previously shown that this cohort of women with CAH in Sweden were less satisfied with the appearance of their genitalia and sexual function (27) and had a reduced pregnancy and delivery rate (28). These factors were correlated with both the *CYP21A2* genotype and, in some respects, the surgical procedure. The aim of this study was to correlate health-related, psychosexual, and psychosocial parameters to the *CYP21A2* genotype and to identify previously unrecognized problems by a qualitative approach in the same cohort of patients.

Patients and Methods

Study population

Sixty-two adult women with CAH aged 18 and 63 (median, 31) yr were included in the study (27–30). The patients were divided into five genotype groups according to the severity of the mildest *CYP21A2* allele: null (n = 14), I2splice (n = 15), I172N (n = 25), V281L (n = 5), and "miscellaneous" (n = 3) genotype groups (Table 1). One patient without genital virilization, diagnosed in adulthood, was included in the V281L group (31). The miscellaneous group consisted of three patients with genotypes that did not fit into any one of the main groups and with a severity between the I172N and V281L groups. These three patients were not included in the statistical analyses of genotype groups. The age did not differ between the groups. Age-matched controls, born the same day, were recruited through the Swedish Population Registry. All but two CAH women and two controls were of Caucasian ethnicity.

Methods

All women were examined as part of a larger follow-up study including endocrine and surgical aspects (27–30). The women filled out a questionnaire and the psychological general well-being (PGWB) formula with no more guidance than a short written instruction. The questionnaire consists of 120 questions (*e.g.* civil status, occupation, leisure activities, sexual orientation, and perceived impact of the disease on their upbringing, schooling, and spare time, as well as their relations with parents, siblings, friends, and partners). They were also invited to make freely formulated comments.

We used information from a Swedish statistical database (www.scb.se) to evaluate the sex distribution in the occupations of the participants in this study. This database provides information on the percentage of men and women in different professions, *e.g.* 0.9% of construction workers are females. The figures were used to calculate the mean female percentage in the occupations held by cases and control women. We defined "male-dominant occupation" as no more than 25% females in the profession and "extreme male-dominant occupation" as no more than 11% females in the profession.

The PGWB index is a QoL instrument with high validity used in many conditions (32, 33). It is a self-assessment inventory of

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TABLE 1. Choice of occupation and leisure activities in the 62 women with CAH and the different *CYP21A2* genotype groups compared to controls

	CAH	Null	I2splice	I172N	V281L	Controls
n	62	14	15	25	5	62
Occupation						
Male dominant	13/43	6/11	3/12	2/17	2/3	6/47
P value (patients *vs.* controls)	0.04	0.006[a]	NS (0.3)	NS (0.7)	NS	
Extreme male dominant	6/43	5/11	1/12	0/17	0/3	1/47
P value (patients *vs.* controls)	0.04	0.0005[b]	NS (0.4)	NS	NS	
Females in occupation (%)	50	35	48	61	41	63
P value (patients *vs.* controls)	0.009	0.01	NS (0.1)	NS (0.6)	NS	
Interests						
Sports	47/57	12/13	10/14	20/25	5/5	41/60
P value (patients *vs.* controls)	NS (0.06)	NS (0.07)[c]	NS (0.5)	NS (0.2)	NS	
Rough sports	42/57	12/13	10/14	17/25	3/5	30/60
P value (patients *vs.* controls)	0.007	0.004[d]	NS (0.1)	NS (0.1)	NS	
Motor vehicles	8/57	4/13	3/14	1/25	0/5	0/60
P value (patients *vs.* controls)	0.002	0.000	0.006	NS (0.3)	NS	

Fisher's exact test was used for the statistic calculations.

[a] Null *vs.* I2splice: $P = 0.2$.

[b] Null *vs.* I2splice: $P = 0.06$.

[c] Null *vs.* I2splice: $P = 0.2$.

[d] Null *vs.* I2splice: $P = 0.2$.

affective or emotional states during the previous week with 22 items (0–5) divided into six subscales: anxiety, depression, health, self-control, well-being, and vitality. A high score represents better outcome. For 50 patients and 31 controls, the last question (appearing on a separate page) was lost. We therefore chose to impute the missing question by using the average result from the completed questions on the same subscale.

Statistical analysis

Statistical analyses were performed for the genotype groups null, I2splice, I172N, and V281L. Nonparametric tests were used. The overall comparisons of *CYP21A2* genotype groups and controls for continuous parameters were analyzed by Kruskal-Wallis test, followed by the *post hoc* Mann-Whitney *U* test. The relationship between continuous parameters and genotype was analyzed by means of the Spearman rank order correlation coefficient. Categorical data were analyzed using the χ^2 test or Fischer's exact test. We used the SPSS 12.0 software (SPSS Inc., Chicago, IL) and considered a *P* value less than 0.05 statistically significant.

Results

Swedish women with CAH were found to present some differences with control women regarding choice of profession, spare time interests, and sexual orientation.

Occupations and interests

Five of the women with CAH and three of the controls were unemployed or had sickness pensions [not significant (NS)]. The remaining women were engaged in studies or work. Male-dominant occupations were more common among patients than controls ($P = 0.04$) (Fig. 1). Between-group analysis yielded significant differences for patients with null mutations only ($P = 0.006$) (Table 1). Five patients in the null genotype group and one in the I2splice genotype group were employed in professions with extreme male dominance (*e.g.* navy, truck driver, and mechanic). Other examples of male-dominant occupations held by CAH patients, but by none of the controls, were

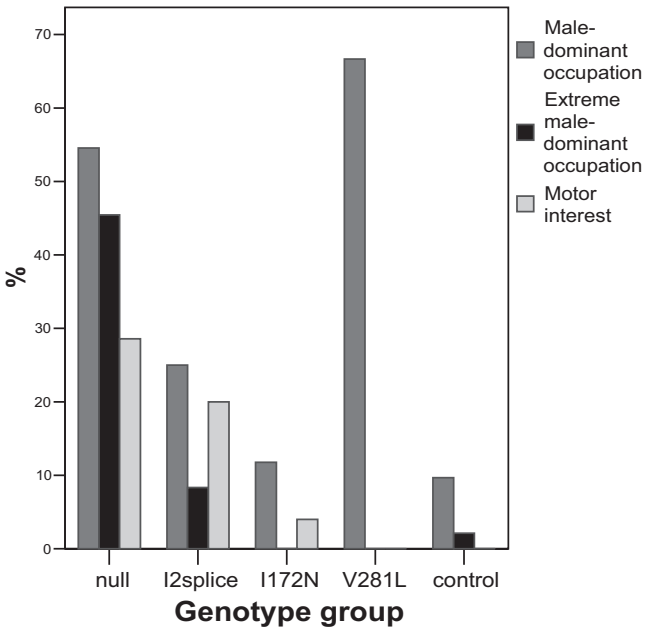

FIG. 1. Male-dominant occupations (≤25% females in occupation), extreme male-dominant occupations (≤11% females in occupation) and motor vehicles as main interest, given as the percentage for the different *CYP21A2* genotype groups and the controls.

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engineer and fitter. The mean percentage of females in occupations among the CAH women correlated with genotype (Table 1) with a correlation coefficient of 0.27 and $P = 0.009$. The overall group difference showed a tendency with $P = 0.06$. Between-group analysis yielded significant differences for patients in the null genotype group compared with the I172N and control groups only ($P = 0.01$).

Significantly more women with CAH reported rough sport and outdoor activities (*e.g.* hockey, soccer) as their main interest during childhood or adult life compared with the control group (Table 1). In fact, patients in the null and I2splice genotype groups practiced exclusively this type of traditionally more masculine sports. Eight women in the CAH group (13%) rated motor vehicles among their top interests ($P = 0.002$) (Table 1 and Fig. 1). All but one of these women belonged to the two severe genotype groups.

Sex and relationships

Fewer women with CAH had a partner (Table 2) (27, 28). The mean age for the sexual debut was 18.7 yr, compared with 16.6 yr in the control group ($P = 0.009$) (28). Eight of the women with CAH (13%) had not debuted sexually ($P = 0.02$) (Table 2), which one woman referred to as "nobody wants someone like me." Four felt that it had to do with "feeling different" or "have not dared to take that step." One woman specifically attributed this to "feeling embarrassed about the appearance of my genitals," whereas another claimed "lack of interest." The mean age of the women who had not debuted sexually was 26 yr (range, 21–32 yr). In comparison, one of the control women had not had a sexual partner.

Thirty-two of the women with CAH (52%) had an active sexual life at the time of assessment, compared with 44 of the control women (71%) ($P = 0.03$). Between-group analysis yielded significant differences for the null genotype group compared with the controls ($P = 0.004$), as well as to the I172N group ($P = 0.02$). Sexual interest was reported by 73% of the women with CAH, compared with 90% of the control women ($P = 0.01$). Between-group analysis was significant only for the null genotype group compared with controls ($P = 0.045$). The lack of interest in sex among cases was ascribed to "looking different," "traces from childhood," or "inability to relax when partner is not told (about the disease)." Patients and controls reported equally good communication with their partner about sexual matters, as well as appreciation of physical closeness. However, half of the women with CAH felt that the disease had had a negative impact on their sex life because of "doubtfulness that it would be practically feasible," "feeling inhibited," "hesitance to tell partner," and "pain and bleeding during intercourse."

Altogether, 10 of 53 women with CAH (19%) and one control stated a homosexual or bisexual orientation ($P = 0.005$) (Table 2 and Fig. 2). In the null group, 50% stated a non-heterosexual orientation, which differed significantly from the other groups except the I2splice genotype group where it did not reach significance ($P = 0.16$), possibly due to the sample size. Nine women with CAH and five of the controls did not answer this question. A statistical sensitivity test, assigning the "no answers" to the bi/homosexual group or to the heterosexual group yielded similar results, with significance for non-heterosexual orientation in the null and I2splice genotype groups and a tendency for significance between null and I2splice ($P = 0.08$). One control was homosexual (2%), which is comparable to a national survey where 2.5% in the Swedish population reported to have had a same-sex partner (www.fhi.se).

TABLE 2. Relationships and sexuality in the 62 women with CAH and the different *CYP21A2* genotype groups compared to controls

	CAH	Null	I2splice	I172N	Miscellaneous	V281L	Controls
n	62	14	15	25	3	5	62
Relationships							
Partner	38 (61%)	4 (29%)	8 (53%)	21 (84%)		2 (40%)	50 (81%)
P value (patients *vs.* controls)	0.01	0.0004	0.04	NS (0.7)		NS (0.3)	
Not debuted sexually	8 (13%)	2 (14%)	5 (33%)	1 (4%)		0 (0%)	1 (2%)
P value (patients *vs.* controls)	0.02	NS (0.09)	0.0008	NS (0.5)		NS	
Sexual orientation							
Heterosexual	43	5	10	21	2	5	56
Bisexual	7	3	2	1	1	0	0
Homosexual	3	2	1	0	0	0	1
Total	53	10	13	22	3	5	57
No answer	9	4	2	3	0	0	5
Bi/homosexual	19%	50%	30%	5%	33%	0	2%
P value (patients *vs.* controls)	0.005	0.0001	0.02	NS (0.5)	NS (0.1)	NS	

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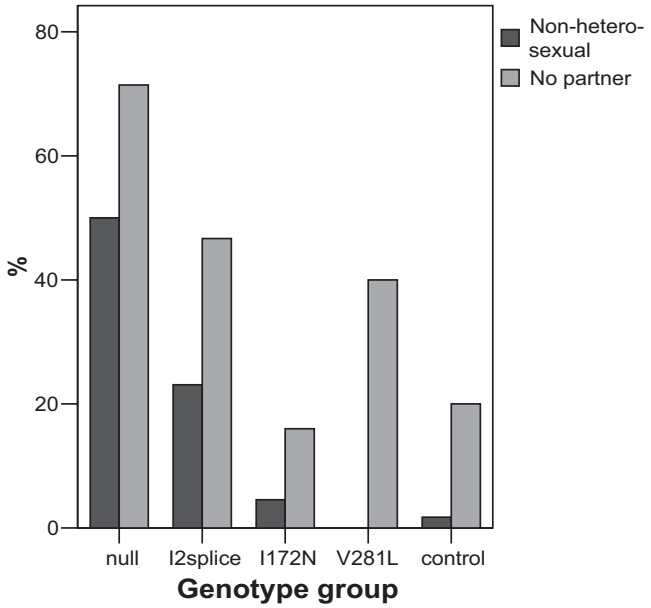

FIG. 2. Women with bi- or homosexual orientation and women with no partner given as percentage for the *CYP21A2* genotype groups and the controls.

Psychosocial adaptation

Half of the women with CAH felt that the disease had influenced their upbringing, *e.g.* "I have been overprotected by my parents" and "I have always felt different." Three women with CAH spontaneously stated that relatives (*e.g.* their mothers) had been ashamed of them. Thirty-five percent meant that the disease had affected their schooling due to "fatigue," "frequent hospital visits," and "inability to attend physical education classes," and 31% that it had had an impact on their spare time for similar reasons. A comparison between the null and I2splice groups combined and the I172N group was significant for affecting schooling ($P = 0.045$) but did not reach significance for spare time ($P = 0.12$).

There were no significant differences regarding interpersonal relationships between the *CYP21A2* genotype groups. Eighteen percent felt that the disease had affected their relationship with their parents, 10% that it had had an impact on the relationship with siblings, and 13% that it had influenced their relationship with peers. The relationship with the partner was even more frequently described as having been affected: 32% stated this and referred to it as "feeling inhibited" or "ashamed of the appearance of my genitals."

The mean (SD) PGWB total score was 77.1 (16.3) for the women with CAH and 79.4 (14.4) for the control group. Although not significant, there was a tendency for differences between the genotype groups ($P = 0.11$). For the different subscales of PGWB, a between-group comparison was significant for "self-control" ($P = 0.04$) and showed a tendency for the subdomain "vitality" ($P = 0.07$). The difference concerning "vitality" was significantly lower for the V281L genotype group compared with all the other groups ($P < 0.02$) except the null group ($P = 0.07$). The domain "perceived general health" did not reach significance with a between-group comparison ($P = 0.12$) but was significant for the null genotype group only ($P = 0.04$).

Discussion

We present data illustrating increased gender-atypical behavior in women with CAH. In several parameters, the magnitude of this change was related to the prenatal androgen exposure. Significant differences were found in choice of profession, spare time interests, civil status, sexual orientation, sexual activity and interest, and health-related QoL issues. This was especially true of patients with null mutations compared with controls, and with a tendency for a difference also between null and I2splice genotype groups. This has not been previously shown, and is particularly interesting because patients in these genotype groups are clinically similar and classified as SW. Our results illustrate that genotyping may add valuable information regarding the life course of the patients and point toward a dose-related rather than a threshold effect. We have previously shown that gender-atypical play behavior is correlated to genotype in girls with CAH in a similar fashion (10).

It was more common for women in the more severe genotype groups to hold a male-dominated job and to have male-typical hobbies, *e.g.* rough sports (Table 1 and Fig. 2). In fact, null and I2splice genotype groups reported exclusively this type of traditionally more masculine sports, which may be regarded as an extension of the rough and tumble play behavior reported for young girls with CAH (4, 9). A prime interest in motor vehicles as stated spontaneously by eight women has not been reported previously. It was recently shown that in SW CAH, the effect size of behavioral differences was as large, or even larger, than that of sex differences between males and females, particularly regarding leisure time activities (13). Our findings support the hypothesis that biologically influenced aspects of gender may be more freely expressed in leisure time activities, comparable to childhood play (13). Parents' expectations, *i.e.* expecting the CAH girls to be more masculinized in their overall behavior, have been argued as one of the explanations for gender-atypical behavior. However, the finding that parents of CAH girls encouraged female-typical behavior more in CAH girls than they did with their unaffected daughters speaks against this as an explanation (34). In addition, we have previously shown that CAH parents rate their girls as more

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masculine in their behavior and would like them to be less so, whereas control parents wished their girls to be more masculine than they were, and, in fact, just as masculine as the CAH parents wished their girls to be (35). Hence, this makes it unlikely that the parents' treatment or expectations would be the cause of this effect.

Our results show an increased non-heterosexual orientation in women with CAH. Half of the women homozygous for null mutations reported a bi- or homosexual orientation showing a dose-related effect also between patients with SW CAH. Previously reported frequencies range from 3 to 31%, but some of these include only a small number of patients (n = 16–34) (7, 12, 15, 18). Patients are commonly classified according to clinical symptoms, which does not distinguish between patients with null and I2splice mutations. Furthermore, it is possible that earlier studies include a larger proportion less severely affected patients because the survival rate historically has been lower among those with the most severe form of the disease. A recent study including 134 CAH women identified a homosexual and bisexual orientation in 16% of women with the SW form and 5% in the SV group (15). Interestingly, an increased frequency of homosexual and bisexual orientation was also found in women with the NC form of CAH, indicating that the relatively mild prenatal androgen excess in NC CAH may be sufficient to influence psychosexual development in some cases, or that the increased postnatal androgen levels before diagnosis can affect sexual differentiation of the brain. Sexual behavior and fantasies according to the Kinsey scale show a progression along with the severity of the disease (7, 12, 15, 18). We used the individuals' own perception of themselves as heterosexual, bisexual, or homosexual, thus failing to record other feasible aspects of sexuality, such as erotic fantasies and sexual experience with a same-sex partner. Nine of the patients and five controls did not answer this particular question, which further underlines the difficulties associated with this topic. Taken together, our results may constitute an underestimation. Although an increase in non-heterosexual orientation must now be considered well established, the reason for this has been under debate. Besides a purely biological explanation, such as imprinting mechanisms of androgens on psychosexual development, several psychosocial aspects should be considered. Many of these patients have undergone genital surgery, in some cases repeatedly. Eleven of our patients had had surgery more than five times, and one had been through 29 surgical procedures, with obvious risks for impaired sensitivity and dissatisfaction with genital appearance and function (27). In addition, one must consider the stress of repeated surgical procedures and genital examinations, which may contribute to an impaired body image.

Fewer women with CAH lived with a partner, and they had children less often. We have previously reported that 23% in this cohort had children (28). Besides the abovementioned factors related to sexuality, this might also be explained by changes in personality characteristics. Women with CAH exhibit detachment (*i.e.* need for distance in social and close relations) (36) and a reduced interest in nurturing (3, 37). In addition to prenatal effects of androgens, these personality changes may relate to some other aspects of the disease. It is possible that childhood gender-atypical behavior in itself hampers later gender-related socialization processes, *e.g.* reducing contact with female peers due to different interests during the formative preadolescent period. Parental treatment, *e.g.* overprotection, may also affect the psychosocial development in children with chronic diseases. Living with a chronic condition may further reinforce the notion of oneself as being different. The same factors may also be related to the later sexual debut, which the women themselves felt had to do with various aspects of the disease, such as feeling different or embarrassed about the look of their genitals.

QoL is difficult to define, both because it is affected by many factors and because there are large individual variations in what one regards as important for a good QoL. We used PGWB as an objective measure of QoL. Interestingly, the domain "perceived general health" differed between cases and controls only in the null genotype group. There were few patients with the NC form of CAH in our sample. However, their low scores on "vitality" prompts speculation that overtreatment and suppressed androgen levels may be of importance. Suppressed levels of androgens were found in this cohort of patients, but not only in the V281L genotype group (29). Exposure to postnatal androgens before diagnosis may also be of importance (13). In general, patients with chronic conditions do not report an impaired QoL, which has been interpreted as a result of the acquirement of coping strategies (24). Although we did not identify a strongly impaired QoL by objective measures, the participants' freely formulated responses in the questionnaire gave a different picture. Many stated that the disease had had a strong negative impact on their life, particularly regarding their sexual life, which more than half of the patients felt had been severely affected by the disease. This illustrates that a qualitative approach may be helpful to identify issues that do not become evident using quantitative methods.

Some of the responses in the questionnaires reflect the challenges faced by many parents to a child with abnormal genitalia. Half of our patients felt that the disease had had

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a severe impact on their upbringing, *i.e.* on parent-child interaction, such as overprotection, shame, and stigma. The patients' own perception of the impact of the disease on issues such as the relationship with parents, siblings, and peers did not correlate with the genotype. This indicates that the level of prenatal androgen exposure is less important for these factors, as suggested previously (22), but relies instead on the families' coping strategies, which further illustrates the need for psychological support and education for parents. The parent-child relationship may, for example, benefit from the information that the prenatal androgen exposure has an effect on play behavior and toy preferences. Parental support at diagnosis of the child as well as continuously during her development is of outmost importance. This is further illustrated by an interview study in which the majority of parents of girls with CAH rated their future sexual orientation as very important, and genital appearance as crucial, for female gender function (38). Providing accurate and understandable information to the parents is essential for psychosocial adaptation, as well as continuous information to the patient at all ages, through puberty and as young adults.

In conclusion, our data show increased gender-atypical behavior regarding professional occupations, spare time interests, and sports, as well as sexual orientation in women with CAH. This was more pronounced in the most severe genotype groups, especially in patients with null mutations. Our results confirm a dose-related effect of prenatal androgen exposure on all the above-mentioned parameters, which becomes evident using the *CYP21A2* classification. Although many QoL-associated factors were impaired, validated instruments measuring QoL and sexual function did not identify large differences. The impact of the disease on upbringing and relationships with family members and friends did not correlate with disease severity, indicating that other factors, such as coping strategies, are important. This illustrates the need for psychological support to parents and patients.

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