CLINICAL STUDY

Quality of life in 70 women with disorders of sex development

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Abstract

Objective: The aim of this study was to assess the quality of life and psychosocial well-being in women with disorders of sex development (DSD).

Design: An open case-control study.

Methods: Social and psychiatric information was collected via a structured interview from 70 Danish women diagnosed with DSD, 70 controls matched on sex, age, and school education, and six women with isolated genital malformations. Quality of life and mental distress were assessed by ‘Quality of Life-Assessment of Growth Hormone Deficiency in Adults’ (QoL-AGHDA) and three symptom scales from the ‘Hopkins Symptom Checklist’ (SCL-90-R; i.e. somatization, depression, and anxiety) respectively. For both measures, higher scores reflected poorer outcomes.

Results: Present relationships and having children were less frequent in patients than in controls (P < 0.02 and P = 0.001 respectively). Previous suicidal thoughts (P = 0.002) and a higher frequency of psychological/psychiatric counseling for severe problems (P = 0.06) were more frequently reported in patients than in controls. The mean QoL-AGHDA score was significantly higher in patients than in controls (5.5 vs 2.9; P = 0.002), especially for congenital adrenal hyperplasia (CAH) females (P = 0.01) and virilized 46,XX and 46,XY females (P = 0.04). The total SCL score was higher in patients than in controls (mean 23.2 vs 20.0), reaching significance for anxiety (mean 6.3 vs 4.3, P = 0.03) with highest score in CAH (P = 0.01).

Conclusion: An impaired quality of life and more affective distress were observed especially in CAH patients and virilized 46,XX and 46,XY females. This may be caused by trauma from distressing diagnostic procedures, the chronic illnesses per se, and psychosocial consequences of the disorders.

Introduction

Disorders of sex development (DSD) encompasses a range of undervirilized 46,XY individuals, overvirilized 46,XX individuals, or true hermaphroditism. If an infant is born with ambiguous genitalia, it will be exposed to numerous diagnostic procedures, including surgery, hormonal treatments, and long-term follow-up, which, in addition to the disease itself, may cause serious distress. Quality of life measures are increasingly being used to determine the impact of medical intervention on function, adjustment, and psychosocial well-being (1). According to The World Health Organization (2), quality of life is defined as the ‘individual’s perception of their position in life in the context of the culture and the value systems in which they live and in relation to their goals, expectations, standards, and concerns’. Quality of life includes six domains: physical, psychological, level of independence, social relationships, environment, and spirituality/religion/personal beliefs. The aim of the present study was to evaluate self-reported quality of life and psychological well-being in adult females diagnosed with either complete androgen insensitivity syndrome (CAIS), a 46,XX or 46,XY karyotype and some degree of virilization (i.e. 46,XX- and 46,XY-virilized females), 46,XY gonadal dysgenesis syndrome (GD), or congenital adrenal hyperplasia (CAH).

Subjects and methods

Population characteristics

Patients This was an adult follow-up study of patients diagnosed with DSD in childhood or adolescence at the University Hospital of Copenhagen (Rigshospitalet) in the period 1953–2003 (n = 70). Patients with a previous contact to the departments of pediatrics, plastic surgery, pediatric surgery, or gynecology were contacted by letter and the participation rate was 81%. In addition, from the same surgical departments, a group of patients (referred to as operated controls) with congenital genital malformations without an established endocrine or genetic diagnosis were recruited to evaluate the long-term effects.
of isolated genital malformations. The participation rate was 31.6% (n = 6).

Eleven patients had CAIS (median age 35.4 years, range 18.3–55.8), of these, ten had verified androgen receptor mutations, including the previous reported mutations R856C, S434F, T861I, 1020delA, and V867M, and the non-reported mutations 2449+1G>C, 1074delG, 450_532dup83, and 1747delT (reference sequence NM_000044) in the androgen receptor database (3). Fifteen patients were virilized 46,XY females (39.0 years, range 21.9–55.2), of which two siblings had genetically verified partial androgen receptor deficiency (i.e. R840H, Table 1); three patients had GD (29.6 years, range 24.6–30.1); and one 46,XX patient was diagnosed with virilization at 4 years of age, without any detectable mutations in the CYP21 gene or the P450 oxidoreductase (POR) gene (33.9 years). The latter was included in the group of 46,XY-virilized females. The CAH group (30.3 years, range 17.9–51.8) consisted of 33 patients with a verified CYP21 mutation (21 salt wasters, 6 simple virilizers, 5 late onset, and 1 patient diagnosed in adolescence), three patients with STAR mutations, one patient with a CYP17 mutation, and three patients (siblings) with mutations in the POR gene (R550W/A287P). Median age at examination in the operated controls was 40.7 years (range 29.2–63.3). Four pairs of siblings were included in the CAH group and three pairs of siblings in the virilized 46,XX and 46,XY groups.

Background data were collected from medical records and included age at diagnosis, sex assignment, genetic work up, medical comorbidity, and frequency of hospitalizations due to medical (not surgical) conditions. Exclusion criteria were mental retardation (n = 3) or that the present physician stated that study participation would cause unacceptable distress (n = 3).

### Table 1  Age and signs of virilization at time of diagnosis in virilized 46,XX (ID 1) and 46,XY females (ID 2–16).

<table>
<thead>
<tr>
<th>ID</th>
<th>Age at diagnosis (years)</th>
<th>Ambiguous genitalia</th>
<th>Clitoris hypertrophy</th>
<th>Other virilization signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td></td>
<td>X</td>
<td>Hirsutism, male voice, male pubic hair demarcation</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>X</td>
<td>X</td>
<td>Male voice</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td></td>
<td>X</td>
<td>Maybe gonads in the labiae</td>
</tr>
<tr>
<td>5</td>
<td>0.8</td>
<td></td>
<td>X</td>
<td>Male voice</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>At birth</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>At birth</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>At birth</td>
<td>X</td>
<td></td>
<td>A gonad in the inguinal region</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td></td>
<td></td>
<td>Gonads in the inguinal regions</td>
</tr>
<tr>
<td>12a</td>
<td>1</td>
<td>X</td>
<td></td>
<td>Gonads in the labiae</td>
</tr>
<tr>
<td>13</td>
<td>4</td>
<td>X</td>
<td></td>
<td>Gonads in the inguinal regions</td>
</tr>
<tr>
<td>14a</td>
<td>8</td>
<td>X</td>
<td></td>
<td>A gonad in the labia</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>X</td>
<td></td>
<td>Gonads in the inguinal regions</td>
</tr>
<tr>
<td>16</td>
<td>0.8</td>
<td>X</td>
<td></td>
<td>Gonads in the labiae</td>
</tr>
</tbody>
</table>

*Verified androgen receptor mutation.*

**Age at diagnosis and sex assignment** The CAIS patients were diagnosed at a median age of 5 years (range 0–22 years), the 46,XX- and 46,XY-virilized females at 3.9 years (range 0–19 years), the CAH patients at 0 year (range 0–16.1 years), the GD patients at 10.0 years (range 9–16 years), and the operated controls at 17.7 years (range 14–20 years). At birth, no male gender assignments were reported in the CAIS or the GD groups. In the group of 46,XY-virilized females, two patients had ambiguous genitalia, but were assigned female gender. For one of these patients, a surgical male reassignment was conducted at the age of 1 year and 5 months – a reassignment that was reversed to female gender at the age of 3 years and 7 months. Signs of virilization at time of diagnosis in the group of virilized females are shown in Table 1. Signs of virilization at time of diagnosis in 35 patients from the CAH group are previously reported (4). In the present study, additionally two salt-wasting CAH patients and three POR patients were included. Both salt wasters were diagnosed at birth; one because of ambiguous genitalia (CYP21del/CYP21del), while data on virilization signs at birth was lacking for the other (Q318X/Q318X). The three POR patients were diagnosed at the age of 3, 0.2, and 0.08 years respectively, the first two patients due to clitoris hypertrophy and the third because of ambiguous genitalia. None of the operated controls had any male gender assignment. In the patients, the degree of virilization taken into account the time of diagnosis was graded on a 1–5 scale: 1, no signs of virilization; 2, signs of virilization signs diagnosed ≥1 year of age; 3, signs of virilization diagnosed <1 year of age; 4, ambiguous genitalia at birth; and 5, severe virilization with male gender
assignment at birth, but gender reassignment to female after diagnosis.

**Medical comorbidity** Significant somatic comorbidity existed in two CAIS patients having insulin-dependent diabetes mellitus and congenital heart disease (i.e. ventricular septum defect) respectively. In the group of 46,XX- and 46,XY-virilized females, two patients were diagnosed with insulin-dependent diabetes mellitus and a pituitary prolactinoma respectively. In the salt-wasting CAH group, one female had cystic fibrosis and another had a unilateral ureteronephrectomia performed.

**Hospitalizations** The median number of hospitalizations in the CAIS females was 1 (range 0–4 hospitalizations), for the 46,XX- and 46,XY-virilized females 2 (range 1–6), for the CAH females 6 (range 0–25), for the GD females 1 (range 1–2), and for the operated controls 2.5 (range 0–5). The hospitalization numbers reflected a minimum, as a complete retrospective collection of medical records was not possible for all the patients.

**Controls** A control group was recruited through the Danish Civil Registration System. For each patient, 20 women living in the Copenhagen area and born in the same month and year as the patient were contacted by a letter containing a description of the study and questions on educational level (i.e. qualifications achieved, total number of completed school years, and vocational training). The response rate of controls was 37.1% corresponding to a mean response from 7.4 controls per patient. The control with the closest match for school education was selected for pairwise matching with the index patient.

**Assessment program**

All patients and controls were administered medical and psychological interviews by a medical doctor and a psychologist respectively. Additionally, the examination program included anthropometrical and gynecological examinations; hormone, chromosome, and mutation analyses; cognitive tests; and questionnaires on personality, sexual, and social functioning. All questionnaires were completed at home, both before (Quality of Life-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA)) and after (the Hopkins Symptom Checklist) clinical examination. The examiners were not blinded with respect to the diagnoses of the included patients.

**Social parameters** Information on the participants’ education and the present employment was collected by a questionnaire on socio-economic status. From items describing type and total number of completed school years, vocational training, present employment, and number of employees, social classes between 1 (highest) and 7 (lowest) were allocated (5). Information on present partnership, presence of children, and previous marital separation was collected.

**Psychiatric parameters** Information on the participants’ previous contacts to psychologist, psychiatrist, and psychiatric departments, previous suicidal thoughts or suicidal attempts, and present psychopharmacological treatment was obtained by interview. Contacts to psychologist or psychiatrist were divided into two categories of severity (mild/severe), depending on reason for and duration of counseling. Participants with no previous contact to the psychiatric/psychological system were asked whether they ever had felt a need for a contact to this system.

**Quality of life** The participants’ quality of life was assessed by a Danish version of the questionnaire QoL-AGHDA (6). The dichotomous (i.e. yes and no) questionnaire contained 25 items, describing lack of assertiveness, concentration, and energy; increased anxiety and depression; and difficulties in social interactions. A total score of maximum 25 was derived from all 25 items, with higher scores denoting a poorer quality of life. For this scale, coefficient α was 0.90. There were four missing responders for this questionnaire (one CAIS patient and three CAH patients).

**Mental distress** The questionnaire on mental distress comprised three scales from the Danish version of the Hopkins Symptom Checklist, SCL-90-R (7). The three self-reported scales were somatization (12 items), depression (13 items), and anxiety (10 items), and a total score was calculated as the sum of the three scores. The five answer categories were ranged from 0 (not at all) to 4 (extremely), a higher score representing a higher degree of distress. Accordingly, maximum scores for somatization, depression, and anxiety were 48, 52, and 40 respectively, and the total score was 140. Coefficient α was 0.95 for the total score, and 0.83, 0.93, and 0.89 for the three subscales respectively. The subject was asked the extent to which each particular symptom had caused malaise during the last week including the day of questionnaire completion. The missing responders for this questionnaire were two CAIS patients, four CAH patients, one operated control, and five healthy controls.

**Statistical analysis** Statistical analyses were conducted by non-parametric tests. The Wilcoxon signed
rank sum test was used in comparisons of patients and matched controls, and Mann–Whitney/Kruskal–Wallis tests in analyses of differences between patient subgroups. In comparisons of groups of unequal size, significance levels were approximated using the Monte Carlo exact test.

**Approvals** Approvals were granted from the local ethical committee (01–051/01.11–075/03), and the Danish Data Registry (2001-41-0689). The study was performed according to the Helsinki declaration II after an obtained written consent from the participants.

### Results

#### Social parameters

Social classes were lower in patients than in controls \((P=0.04)\), especially in the virilized 46,XX and 46,XY females \((P=0.05)\). No differences were observed between the remaining patient subgroups and their matched controls \((P=0.20–0.49)\), between patient and operated controls \((P=0.65)\), between control groups \((P=0.38)\), or between patient subgroups \((P=0.26)\), Table 2).

Overall, present relationships were significantly less frequent in patients \((n=41)\) than in controls \((n=54, P=0.02)\), Table 2). This finding was due to less frequent partnerships in the CAIS and CAH females, as compared with their matched controls \((P=0.03\) and 0.06 respectively). Significant differences were also demonstrated between patient subgroups \((P=0.01)\). The operated controls did not differ from patients or healthy controls \((P=0.40\) and 1.0 respectively). Homosexual relationships were reported in five CAH patients (four salt wasters and one POR patient), while none of the controls had a same sex partner. Marital separations were overall less frequent in patients \((n=6)\) than in controls \((n=12, P=0.11)\), but there were no differences in the frequency of marital separations between any groups \((P=0.13–1.0)\).

### Psychiatric parameters

A tendency towards a higher frequency of counseling due to severe symptoms was found in the patient group as compared with their matched controls \((P=0.06)\), Table 3), while no differences were shown between any groups with respect to counseling due to mild symptoms \((P=0.21–1.0)\), or previous psychiatric hospitalizations \((P=0.16–1.0)\).

Previous suicidal thoughts were reported significantly more frequent in the patient group \((n=26)\) and in the operated controls \((n=3)\), as compared with the healthy controls \((n=9)\), \(P=0.002\) and 0.05 respectively. Previous suicidal thoughts were distributed unevenly among patients with higher frequencies in the 46,XX- and 46,XY-virilized females \((P=0.008)\) and CAH females \((P=0.03)\), as compared with their controls, while the CAIS and GD females had lower frequencies. The frequency of suicidal thoughts did not differ between patients and operated controls \((P=0.67)\) or between patient subgroups \((P=0.11)\). A history of suicidal attempt was reported in 11.6% of the patients and 4.3% of their controls, but in none of the operated controls. Median age at first suicidal attempt was 19.5 years (range 16–34) in the patients and 18.0 years (range 17–19) in the controls. Among patient subgroups, suicidal attempts were primarily seen in the CAH group \((P=0.10)\) as compared with their controls, but no significant differences in previous suicidal

### Table 2

Social classes based on educational level and present employment, and percentages of present relationships, marital separations, and children (biological or adopted) in patients with DSD conditions.

<table>
<thead>
<tr>
<th></th>
<th>Social class median (range)</th>
<th>Present relationship (%)</th>
<th>Marital separation (%)</th>
<th>Children (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAIS</td>
<td>11</td>
<td>4.0 (1–6)</td>
<td>27.3*</td>
<td>10.0*</td>
</tr>
<tr>
<td>Virilized females</td>
<td>16</td>
<td>4.0 (1–7)*</td>
<td>81.3</td>
<td>6.3</td>
</tr>
<tr>
<td>CAH</td>
<td>40</td>
<td>4.0 (1–7)</td>
<td>55.0</td>
<td>10.0</td>
</tr>
<tr>
<td>GD</td>
<td>3</td>
<td>3.0 (1–3)</td>
<td>100.0</td>
<td>0</td>
</tr>
<tr>
<td>All patients</td>
<td>70</td>
<td>4.0 (1–7)*</td>
<td>58.6*</td>
<td>8.7*</td>
</tr>
<tr>
<td>Matched controls</td>
<td>70</td>
<td>3.5 (1–7)</td>
<td>77.1</td>
<td>17.1</td>
</tr>
<tr>
<td>Operated controls</td>
<td>6</td>
<td>4.0 (2–7)</td>
<td>83.3</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Significance levels for differences between patients and matched controls are indicated as *\(P<0.05\), †\(P<0.01\), or ‡\(P<0.001\). CAIS, complete androgen insensitivity syndrome; virilized females, 46,XX karyotype \((n=1)\) or 46,XY karyotype \((n=15)\) and virilization; CAH, congenital adrenal hyperplasia; GD, gonadal dysgenesis syndrome; and operated controls, patients with congenital genital malformations without known endocrine etiology.

*Missing data in one CAIS patient.

www.eje-online.org
The Hopkins Symptom Checklist, SCL-90-R

**Total score** Although not statistically significant, the total SCL score in the patients was higher than in the matched controls ($P=0.11$), especially for the CAH group ($P=0.09$), while the CAIS females had lower score than healthy controls. No other differences were found between any groups ($P=0.18–1.0$).

**Somatization** No statistical differences in mean somatization scores were found in the patients versus the two control groups ($P=0.31–0.80$), between patient subgroups ($P=0.10$) or between controls ($P=0.30$).

**Depression** Although not statistically significant, the patients demonstrated a higher mean depression score than the control group ($P=0.13$), mostly pronounced in the CAH group ($P=0.07$), while CAIS females had lower scores. No other differences were found between any groups ($P=0.35–1.0$).

**Anxiety** The mean anxiety score was significantly higher in the patients than in the controls ($P=0.03$) with the largest difference found between CAH females and their controls ($P=0.01$), while CAIS females had lower scores. None of the other patients differed significantly from their paired controls ($P=0.41–0.92$). The operated controls did not differ from patients ($P=0.71$), or from healthy controls ($P=0.89$).

For both the QoL-AGHDA and the SCL-90-R questionnaires, statistical analyses were repeated with exclusion of the seven pairs of siblings one at a time to evaluate the potential effects of correlated observations. These analyses showed essentially the same results (data not shown).

In the patients, the correlation $r_s$ between total QOL-AGHDA score and the degree of virilization at time of

Quality of Life-Assessment of Growth Hormone Deficiency in Adults, QoL-AGHDA

The QoL-AGHDA score of 5.5 in the patients was significantly higher than in the controls (2.9, $P=0.002$, Table 4). The QoL scores varied between patient groups, as the highest mean scores were seen in the CAH- and the 46,XX- and 46,XY-virilized groups compared with controls ($P=0.01$ and 0.04 respectively), while the CAIS females had lower scores than the controls. No significant differences were found for the other subgroups versus their controls ($P=0.41–0.95$). The mean score of 4.3 in the operated controls did not differ from the patients or the healthy controls ($P=0.43–0.77$).

Table 3 Psychiatric parameters in patients with disorders of sex development.

<table>
<thead>
<tr>
<th></th>
<th>CAIS Virilized</th>
<th>CAH</th>
<th>GD</th>
<th>All patients</th>
<th>Matched controls</th>
<th>Operated controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>11</td>
<td>16</td>
<td>40</td>
<td>3</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td><strong>Previous contact to psychiatrist/psychologist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe symptoms (%)</td>
<td>20.0$^a$</td>
<td>25.0</td>
<td>27.5</td>
<td>33.3</td>
<td>26.1$^a$</td>
<td>14.3</td>
</tr>
<tr>
<td>Mild symptoms (%)</td>
<td>0$^a$</td>
<td>12.5</td>
<td>17.5</td>
<td>0</td>
<td>13.0$^a$</td>
<td>11.4</td>
</tr>
<tr>
<td>No; subjective need (%)</td>
<td>50.0$^a$</td>
<td>25.0</td>
<td>21.1</td>
<td>0</td>
<td>25.7$^e$</td>
<td>22.9</td>
</tr>
<tr>
<td>Previous psychiatric hospitalizations (%)</td>
<td>0$^a$</td>
<td>12.5</td>
<td>7.5</td>
<td>0</td>
<td>7.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Previous suicidal thoughts (%)</td>
<td>10.0$^a$</td>
<td>43.8</td>
<td>45.0</td>
<td>0</td>
<td>37.7$^a$</td>
<td>12.9</td>
</tr>
<tr>
<td>Previous suicidal attempts (%)</td>
<td>0$^a$</td>
<td>6.3</td>
<td>17.5</td>
<td>0</td>
<td>11.6$^a$</td>
<td>4.3</td>
</tr>
<tr>
<td>Present psychopharmacological treatment (%)</td>
<td>0$^a$</td>
<td>18.8</td>
<td>15.4</td>
<td>0</td>
<td>13.2</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Significance levels for differences between patients and matched controls, and between operated and healthy controls are indicated as $^*P<0.05$. CAIS, complete androgen insensitivity syndrome; virilized females, 46,XX karyotype ($n=1$) or 46,XY karyotype ($n=15$) and virilization; CAH, congenital adrenal hyperplasia; GD, gonadal dysgenesis syndrome; and operated controls, patients with congenital genital malformations without known endocrine etiology.

aMissing data in one CAIS patient.
bMissing data on one virilized female.
cMissing data on one CAIS patient and one virilized female.
dMissing data on one CAH patient.

together with benzodiazepine for dyssomnia, and tricyclic antidepressants, and two other healthy controls were medicated with SSRI for depression and borderline psychosis. One operated control was medicated with levopromazine, carbamazepine, and an NaRI preparation (a noradrenergic and specific serotonergic anti-depressive preparation). Of those, five were treated for depression, and one for both depression and obsessive-compulsive disorder. In the 46,XX- and 46,XY-virilized group, one patient was medicated with SSRI for depression, one with SSRI and levopromazine for anxiety, and one with benzodiazepine, ziprasidone, orphenadrine, levopromazine, carbamazepine, and an NaRI preparation (a selective noradrenergic reuptake inhibitor) for depression and borderline psychosis. One operated control and two healthy controls were medicated with SSRI for depression, and two other healthy controls were treated with benzodiazepine for dyssomnia, and tricyclic antidepressants for tension headache respectively.
Table 4: Quality of Life-Assessment (QoL-AGHDA), as well as total and subscale scores (somatization, depression, and anxiety) from the Hopkins Symptom Checklist (SCL-90-R) in patients with disorders of sex development.

<table>
<thead>
<tr>
<th></th>
<th>QoL-AGHDA scorea</th>
<th>SCL-90-R scoresb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Somatization</td>
</tr>
<tr>
<td>CAIS</td>
<td>1.9 (0–5)</td>
<td>9.8 (1–30)</td>
</tr>
<tr>
<td>Virilized females</td>
<td>7.5 (0–22)</td>
<td>26.4 (0–78)</td>
</tr>
<tr>
<td>CAH</td>
<td>5.8 (0–19)</td>
<td>25.6 (1–115)</td>
</tr>
<tr>
<td>GD</td>
<td>3.0 (0–5)</td>
<td>18.7 (5–26)</td>
</tr>
<tr>
<td>All patients</td>
<td>5.5* (0–22)</td>
<td>23.2 (5–115)</td>
</tr>
<tr>
<td>Matched controls</td>
<td>2.9 (0–23)</td>
<td>18.8 (0–106)</td>
</tr>
<tr>
<td>Operated controls</td>
<td>4.3 (0–11)</td>
<td>20.0 (9–39)</td>
</tr>
</tbody>
</table>

Significance levels for differences between patients and matched controls are indicated as *P<0.05. Scores are given as mean (ranges) with higher scores denoting poorer outcomes. CAIS, complete androgen insensitivity syndrome; virilized females, 46,XX karyotype (n=1) or 46,XY karyotype (n=15) and virilization at birth; CAH, congenital adrenal hyperplasia; GD, gonadal dysgenesis syndrome; and operated controls, patients with congenital genital malformations without known endocrine etiology.

*aMissing data in one CAIS patient and three CAH patients.

*bMissing data on two CAIS patients, four CAH patients, five healthy controls, and one operated control.

diagnosis was 0.38 (P=0.002). Correlations between degree of virilization and SCL-90-R scores were for the total score: r = 0.30 (P=0.02), the somatization score: r = 0.31 (P=0.01), the depression score: r = 0.29 (P = 0.02), and the anxiety score: r = 0.28 (P=0.02). There was a significant correlation between previous suicidal thoughts and the degree of virilization at time of diagnosis (r =0.34, P=0.005).

Discussion

The present study revealed an overall impaired self-reported quality of life, a higher degree of mental distress, and a higher frequency of suicidal thoughts in women diagnosed with DSD. Differences in life quality were observed among patient groups, as CAIS and GD women had better life quality scores than virilized 46,XX and 46,XY females and CAH females. This study furthermore demonstrated a strong tendency towards a higher degree of mental distress and poorer quality of life, the more virilized the patients were at time of diagnosis. Although not significant, the operated controls also showed an impaired quality of life as compared with healthy women, indicating that genital malformations per se may cause psychological problems.

Quality of life in patients with DSD has been evaluated in several studies, primarily with positive results, i.e. the patients did not differ from controls or the background population. Recently, a study of 50 adult patients with DSD conditions reported overall positive psychosocial and psychosexual outcomes (8), although some problems with sexual activity were described. However, their control groups consisted of adult patients with other chronic diseases; i.e. Mb, Hirschsprung and insulin-dependent diabetes mellitus respectively. Thus, this study showed that DSD did not result in additional distress compared with other chronic diseases, but it did not show that quality of life was normal in all aspects. In another study, a higher self-reported quality of life was found in adult patients with classical CAH (16 females and 16 males) than in the general population (9). However, as the participation rate was only 55%, the authors took into account that depressed or socially more isolated patients may have been underrepresented. Additionally, in a study of 21-hydroxylase deficient CAH women (n=45) and controls selected from hospital staff and their families and matched according to age, school education, and professional background, no overall differences in quality of life were reported, despite a higher frequency of living alone and having less children in the patient group (10). In a study of 46,XY individuals with ambiguous genitalia (18 females and 21 males, mean age 34 years) either male or female sex of rearing was concluded to lead to a successful long-term outcome for the majority of patients (11). However, the majority of women (67%) received counseling for issues concerning their diagnosis. Thus, our study is at variance with previous studies on quality of life outcomes. However, the large number of participants, the high participation rate, and especially the inclusion of controls matched for education, strengthen our findings considerably.

The varying quality of life outcomes may reflect various factors. In a previous study, health-related quality of life was analyzed by reviewing available data on a broad spectrum of DSD conditions ranging from simple hypospadias to salt-wasting CAH and cloacal extrophy (12). Substantial differences in impact on

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psychological functioning among syndromes, marked variability's in severity within syndromes, and existence of syndrome- and treatment-specific characteristics were observed. Additionally, despite impairments, patients have been suggested to develop coping strategies for maintaining a high quality of life (10).

We cannot exclude that our findings may be due to differences in methodology, as compared with other studies. The QoL-AGHDA questionnaire was primarily developed for growth hormone deficient patients, in whom the characteristic symptoms, i.e. reductions in muscle volume, decreased exercise capacity, changed body mass, low energy, low initiative, lack of concentration, and memory difficulties (13), may adversely influence quality of life. Similar symptoms are, however, also characteristic for patients suffering from sex hormone disorders or cortisol disturbances, and the QoL-AGHDA was therefore considered useful as a model for quality of life in our patients. As QoL-AGHDA, SCL-90-R, and the results of social and psychiatric parameters supported each other and fitted with the clinical impression of the individuals, we believe that our results are reliable. Despite the high participation rate among patients (i.e. CAH, 83.8%; CAIS, 68.8%; virilized 46.XX and 46,XY females, 100%; and GD, 50%), we cannot exclude selection bias. Thus, a small number of individuals were considered by their present physician to be too frail to participate. It is reasonable to assume that this minor selection would only lead to underestimation of the difference between cases and controls. As patients were recruited from a University Hospital, they may not be representative for the entire DSD population. As the patient group was heterogeneous, one may expect different outcomes depending on phenotype and age at diagnosis. In addition, surgical and hormonal treatment regimens have changed considerably within the last decade, and an age cohort effect cannot be excluded. The operated controls were older at both diagnosis and examination and due to their very small sample size, results in this group need to be interpreted with great caution. The low participation rate among the healthy controls may have induced a selection bias towards either inclusion of controls with poorest outcomes (i.e. thereby giving the lowest estimate of differences between patients and controls) or controls with best outcomes (i.e. thereby over-estimating the real difference between patients and controls). We have no data on none-participants among controls and can therefore not analyze this bias. However, a large potential bias in the assessment of life quality was removed by matching for education. The lack of blinding of the examiners may also influence our data. However, the phenotype and the medical history of the patients excluded a complete blinding, and for the same reason it was obvious, who the controls were.

In the present study, a generally higher degree of mental distress was revealed in especially the virilized 46,XX and 46,XY females and the CAH females, while the CAIS females exhibited better outcomes. Higher SCL scores, i.e. more worse outcomes, are well in line with a previous study based on another questionnaire reflecting mental distress, the Symptom Rating List, in which females with idiopathic hirsutism and/or polycystic ovary syndrome displayed significantly higher levels of anxiety, as compared with a control group matched upon gender, age, marital status, and social class (14). The much better outcome in the CAIS females than in the CAH patients and the virilized women may suggest a clearer gender identity due to female gender assignment at birth, less diagnostic procedures, and a more straightforward treatment.

Mental distress may be viewed as the response to a stressful event (15); therefore, the higher SCL findings in some of the patient groups in the present study may be an expected outcome, and some of the insignificant comparisons in Table 4 may reflect poor statistical power due to sample size. A negative correlation between social class and SCL score, i.e. a higher psychological well-being in the upper class, has previously been reported in a study on mental distress in the Danish general population (16). However, no correlations between social class and total SCL score were observed for the 46,XX- and 46,XY-virilized females and the CAH females in the present study (data not shown). The SCL scores of our controls are well in line with SCL scores reported in a previous study of 618 females representative for the general Danish population (17). This strengthens our findings that especially the virilized females and the CAH females had higher depression and anxiety scores than the controls. To our knowledge, SCL data have not previously been reported in DSD patients, but in an outcome study of patients with micropenis the SCL questionnaire failed to identify any differences in psychopathology between patients and controls (18). However, a comparison of these results with our results is difficult as patients diagnosed with micropenis not necessarily develop gender identity crisis.

The patients, especially CAH and virilized females, reported more frequently suicidal thoughts, severe mental problems, the need for psychological counseling, and present psychopharmacological treatment, as compared with the controls. Mass signficance may be a significant source of over-interpretation, if multiple tests are performed. However, as all results showed comparable patterns, whether significant or not, our findings make sense from a biological point of view.

Previous studies on mental health in patients with DSD are few (12, 19, 20). In a previous study, no differences in psychopathology were observed between CAH girls and controls (21), although CAH mothers reported that their daughters had significantly higher degrees of somatic complaints and schizoid/obsessive traits. The lack of psychopathology was attributed to successful reconstructive surgery, close steroid monitoring, and appropriate emotional support. However, in
a more recent study, general psychopathology (excluding gender identity disorders) was found in 39% of children with DSD, a phenomenon occurring twice as often in patients with no psychological counseling at time of diagnosis (22). Especially, the latter finding supports the present state of the art in treatment of patients with DSD, that psychological counseling should be an integrated part in the professional support. Explanations for a higher degree of psychopathology in the DSD group included the confrontation with developmental interferences, such as sex reassignment procedures, hospitalizations, genital operations, life-long dependence on hormone substitutes, and infertility (22). In a study of CAIS females, the majority (i.e. 83%) had received psychological counseling at some time (23).

From a social perspective, the patients differed significantly from their healthy controls with less frequent relationships and a higher percentage of childlessness. Similar findings have been reported in both CAH patients (10, 24), and in 46,XY females with ambiguous genitalia (11), while CAIS females, in contrast, have been reported to be married and mothers by adoption (19, 23). In the present study, the patients’ own explanations for the lower rate of children were chronic condition, infertility, and factors surrounding relationship. Similar explanations in especially CAH patients have previously been reported (10, 25), in addition to the suggestion of a lack of ‘maternalism’, i.e. a lower interest in getting married and performing the traditional childcare/housewife roles (26). Our study was not designed to determine reasons for social differences. However, as the social parameters support the results from both the self-reported questionnaires and the reported suicidal behavior patterns, we speculate that they reflect another aspect of an affected life quality in the patients.

Conclusion

In this study, of adult women diagnosed with DSD an impaired quality of life was observed in especially CAH women and 46,XX- and 46,XY-virilized women. These findings may reflect the effect of exposure to numerous diagnostic procedures, as well as psychosocial consequences of the disorder per se. Thus, with the aim of reducing the degree of social and psychological problems and improving patients’ quality of life, psychological counseling should be available to all patients diagnosed with DSD or CAH and their families.

References


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