Hypothalamic–pituitary–gonadal axis function after successful kidney transplantation in men and women

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BACKGROUND: Renal transplantation (RT) is the most common solid organ transplant procedure. Several studies have reported on gonadal function in male and female RT recipients with controversial results.

METHODS: Forty consecutive patients (20 male, 20 female) with a fully functioning allograft (serum creatinine 0.8–1.3 mg/dl) for at least 15 months after RT were included in the study. Their ages ranged from 23 to 44 years (median 38) and their post-RT follow-up lasted 15–86 months (median 23). FSH, LH, prolactin, 17-β-estradiol, testosterone, androstenedione and dehydroepiandrosterone were determined in all patients and compared with a group of 80 healthy subjects. Pelvic ultrasonography was performed in all participants.

RESULTS: Testosterone was below the normal range in 70% of male patients and within the lowest third in the remainder; a lack of LH increase indicated an inhibition of the reproductive axis. Male testosterone values were negatively influenced by calcineurine inhibitors treatment (P < 0.005), but positively influenced by a better graft function (P < 0.0001). Testicular and prostate volumes were reduced with respect to controls, with the latter related to circulating testosterone levels. Ten of the women (50%) had menstrual cycle disorders after RT, three being affected by transient, and three by persistent, amenorrhea. Another two patients had had transient polymenorrhea. In four women (20%), a premature ovarian failure was diagnosed. No relationship was found between female reproductive function and age, graft function or duration of the post-transplant period. Prolactin was lower in patients on calcineurin inhibitors (P < 0.01).

CONCLUSIONS: Abnormalities of the reproductive system were frequent after successful RT in both genders.

Key words: amenorrhea/hyperprolactinaemia/normogonadotrophic hypogonadism/premature ovarian failure/renal transplant

Introduction

Currently, renal transplantation (RT) is the most common solid organ transplant procedure. Its growing success is due principally to improved immunosuppressive treatments, resulting in 1- and projected 10-year graft survival rates of 89 and 51%, respectively (Cecka, 2002).

The period of chronic renal failure preceding RT has, however, deleterious consequences on the hypothalamic–pituitary–gonadal (HPG) axis in both genders. In uraemic men, there is an impairment of germinal and Leydig cell function (Lim and Fang, 1975), abnormal GnRH pulsatility (Palmer, 1999), high LH values, low testosterone levels and reduced spermatogenesis (Lim and Fang, 1975; Baumgarten et al., 1977). Prolactin levels are increased due to both a decreased metabolic clearance and an (~3-fold) increased production (Lim et al., 1980; Sievertsen et al., 1980). Data on gonadal function in female patients with chronic renal failure are less clear, but amenorrhea or oligomenorrhea associated with anovulation and decreased 17-β-estradiol (E2) secretion were reported frequently (Holley et al., 1997). These disorders were explained mostly by a hypothalamic dysregulation inducing an abnormal release of FSH and LH (Lim et al., 1980; Ferraris et al., 1987).

Although abnormalities in the HPG axis during chronic renal failure are well recognized in both genders (Handelsman and Dong, 1993; Palmer, 1999), discordant data are available after RT. In particular, male and female HPG dysfunction was found to be either reversed (Ferraris et al., 1987; Samojlik et al., 1992; De Celis and Pedron-Nuevo, 1999), differently improved (Prem et al., 1996; Akbari et al., 2003) or persistently altered after successful RT (De Besi et al., 1988; Talbot et al., 1990).

The HPG axis after RT is mostly influenced by the quality of allograft function, the use of immunosuppressive treatments and general health conditions (Koutsikos et al., 1990; Kokot and Wiseck, 1996). Most previous studies on endocrine function after RT are from 1980–1990 when gonadal function...
was studied during steroid, azathioprine (AZA) and, more rarely, cyclosporin A (CsA) treatments (Handelsman et al., 1982; Ramirez et al., 1991; Peces et al., 1994; Rodriguez-Rodriguez et al., 1996), while the effect of more recent immunosuppressive treatments is not clear.

The optimal life-long maintenance therapy after RT has not been established unequivocally, and protocols with different drug associations are commonly used in clinical practice. Corticosteroids and AZA were the first immunosuppressive agents used until the 1980s. Subsequently, CsA and mycophenolate mofetil (MMF), tacrolimus (TAC) and, more recently, rapamycin were introduced into clinical practice. MMF has been developed recently to replace AZA for maintenance regimens, with positive results on the incidence of rejection. TAC has 10-fold greater immunosuppressive effects than CsA, with reduced adverse effects (Vincenti, 2003): both compounds inhibit T-cell differentiation and programmed cell death, probably promoting the development of self-tolerance.

This cross-sectional study was designed to evaluate the HPG axis function in 40 young adults at least 15 months after successful RT, investigating potential risk factors for HPG axis disorders.

### Materials and methods

#### Patients

Only patients with a fully functioning allograft (creatinine levels <1.5 mg/dl) at least 15 months after RT were included in this study. Forty consecutive patients (20 female, 20 male) met the inclusion criteria and entered the study. Patient characteristics are shown in Table I. Their age at transplantation ranged from 23 to 44 years (median 38) and their post-RT follow-up lasted 15–86 months (median 23). Underlying disease was glomerulonephritis (membranous, segmented or mesangial) in 16 patients, autosomonic polycystic kidney disease (APKD) in five, bilateral reflux due to ureteral malformation in four, glomerulosclerosis in two, micropolyarteritis in one and undiagnosed/unknown in 12 patients. The mean period of dialysis prior to RT was 36 months (range 0–120). Most patients had received RT from a cadaver (n = 38) donor, while two allografts were obtained from living related donors. Satisfactory kidney function was determined by serum creatinine levels (median 1.1 mg/dl; range 0.7–1.3) and calculated glomerular filtrate rate (GFR) (median 85 ml/min; range 60–171). All patients had had puberty at physiological age and had regular gonadal function before the onset of chronic renal failure. No patient had had any rejection episode during the post-transplant period up to study entry.

Results of endocrine and ultrasonographic evaluation were compared with those of 80 healthy controls matched for age, gender and body mass index (BMI).

#### Immunosuppressive regimens

All patients were on maintenance, combined immunosuppressive therapy, stable for at least 6 months. Two immunosuppressive agents were used in 23 patients and three in 17 patients. In detail, all patients were receiving prednisone treatment, while calcineurin inhibitors (CsA and/or TAC) were used in 28 patients and 18 subjects were on MMF or AZA (Table II).

The protocol for corticosteroid dosing remained constant throughout the years: in all patients, a 500 mg dose of methylprednisone (MPD) was given i.v. during RT, followed by the first post-RT dose of 250 mg/day i.v. on the first post-transplant day, then the dose was tapered as follows: 200 mg i.v. on the second day, 125 mg i.v. on the third day, 75 mg i.v. on the fourth day and 50 mg i.v. on the 5th day. From the sixth day after RT, oral prednisone was initiated at a dose of 16 mg daily, maintained up to the third month at the same dose, reduced to 12 mg daily throughout the third and fourth months, to 10 mg daily during the fourth to the fifth month, and to 8 mg daily subsequently. AZA was given at the same dose in all patients for the entire period of post-transplant follow-up; it ranged from 1 to 2 mg/kg daily in a single administration.

CsA and TAC were given by the oral route in two administrations according to protocols based on blood concentrations determined just before the morning dose (trough levels); CsA was started at a dose of 8–10 mg/kg/day and TAC at a dose of 0.15 mg/kg/day. The following trough levels were maintained for CsA: 200–250 ng/ml during the first 2 months, 150–200 ng/ml from the second to the sixth month, and 100–150 ng/ml thereafter. TAC trough levels were 10–15 ng/ml during the first 6 months post-RT and 8–10 ng/ml thereafter. MMF was administered only in associations as a third immunosuppressive agent from 1 week after RT at a dose of 1.5–2 g daily.

#### Study design

All women with regular menstrual cycles were evaluated in the early follicular phase (days 3–6). Previous medical records were reviewed to obtain complete information on patients’ outcome including data on menstrual history pre- and post-transplantation. Informed consent was obtained from all patients, and the design of the study was in accordance with the Declaration of Helsinki.
Table III. The hypothalamus–pituitary–testis axis in 20 men after RT (median and range)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 20)</th>
<th>Controls (n = 40)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (IU/l)</td>
<td>5.4 (1–16)</td>
<td>4.8 (1–10)</td>
<td>2–10 IU/l</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>5.25 (2–19)</td>
<td>4.7 (2–3)</td>
<td>2–10 IU/l</td>
</tr>
<tr>
<td>Prolactin (mg/l)</td>
<td>7 (5–13)</td>
<td>8 (5–16)</td>
<td>5–18 µg/l</td>
</tr>
<tr>
<td>17-OHP (nmol/l)</td>
<td>11.2 (5.8–14.5)</td>
<td>2.4 (3.5–8.0)</td>
<td>0.3–7.6 nmol/l</td>
</tr>
<tr>
<td>Androstenedione (nmol/l)</td>
<td>3.14 (2.4–9.8)</td>
<td>5.6 (3.5–8.0)</td>
<td>3.5–9.4 nmol/l</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>11.6 (4.8–18.4)</td>
<td>23.2 (13.9–31)</td>
<td>12.1–31 nmol/l</td>
</tr>
<tr>
<td>17β-estradiol (pmol/l)</td>
<td>77.1 (66.1–88.1)</td>
<td>91.8 (66–110)</td>
<td>&lt;147 pmol/l</td>
</tr>
<tr>
<td>Dehydroepiandrosterone</td>
<td>0.7 (0.5–4.2)</td>
<td>6.8 (2.7–14.1)</td>
<td>&lt;2.17–15.2 µmol/l</td>
</tr>
<tr>
<td>sulphate (nmol/l)</td>
<td>0.7 (0.5–4.2)</td>
<td>6.8 (2.7–14.1)</td>
<td>&lt;2.17–15.2 µmol/l</td>
</tr>
<tr>
<td>Men with testosterone</td>
<td>14 (70%)</td>
<td>0 (–)</td>
<td>–</td>
</tr>
<tr>
<td>below the normal range</td>
<td>6/–/–</td>
<td>8/22/10</td>
<td>–</td>
</tr>
<tr>
<td>Men with testosterone in</td>
<td>14 (70%)</td>
<td>0 (–)</td>
<td>–</td>
</tr>
<tr>
<td>the normal range territories</td>
<td>6/–/–</td>
<td>8/22/10</td>
<td>–</td>
</tr>
<tr>
<td>Prostate volume (cm³)</td>
<td>11.8 (8.3–16.2)</td>
<td>19.7 (16.8–21.5)</td>
<td>–</td>
</tr>
<tr>
<td>Testicular volume (cm³)</td>
<td>11.1 (5.8–14.8)</td>
<td>16.7 (13.5–20.6)</td>
<td>–</td>
</tr>
</tbody>
</table>

*P < 0.05 versus controls.  
*bP < 0.01 versus controls.  
*cProstate and testicular volumes were calculated as (cranio-caudal × transverse × antero-posterior diameter × 0.52); the mean of right and left volumes was considered as the testicular volume.

Endocrine evaluation

Blood samples were obtained between 8 and 10 a.m. Circulating FSH, LH, testosterone, E₂, 17α-hydroxyprogesterone (17-OHP), Δ4-androstenedione and dehydroepiandrosterone sulphate (DHEA-S) were measured in all patients in a single sample, while prolactin was measured during a 2 h profile (six samples taken every 20 min). All samples were stored at −80°C until assayed altogether. All measurements were performed by commercially available kits within the same assay: testosterone, E₂ and DHEA-S using Immulite, solid phase chemoluminescent enzyme immunoassay (from DPC, Los Angeles, CA); FSH and LH with a radioimmunoassay from Biodata S.p.A. (Rimini, Italy); and androstenedione and 17-OHP with a radioimmunoassay from Diagnostic Systems Laboratories (Webster, TX). Intra-assay coefficients of variation were <7% for all determinations.

Ultrasonographic evaluation

Ultrasonographic testicular examination and transrectal ultrasonography of the prostate gland were performed in all male participants with transducers operating at a frequency of 7.5 MHz. Transparietal pelvic ultrasonography was performed in all women, using a 3.5 MHz linear transducer. Prostate, testicular and ovarian volumes were calculated according to to the ellipsoid formula (antero-posterior × transversal × cranio-caudal diameter × 1/3 π).

Statistical analysis

Paired Student’s t-test was used to compare patients versus controls. The non-parametric method (Mann–Whitney U-test) was used when the results of Wilk-Shapiro’s test were not consistent with the Gaussian distribution of the data. The χ² test was used to associate

endocrine disorders with clinical features. Age, gender, time elapsed from RT, dialysis duration, kidney function expressed as GFR and creatininaemia, type of immunosuppressive regimen and corticosteroid dose were considered as possible influencing factors for HPG axis function. Since most of the patients' data had a skewed distribution, median and range were used throughout the text and in the tables. Significance was set at 5%.

Results

The male HPG axis after RT (Table III)

Testosterone, DHEA-S and androstenedione levels were significantly lower, while 17-OHP levels were significantly higher in the patients than in controls (P < 0.05). Prolactin, E₂ and gonadotrophin levels were similar in the two groups. Testosterone levels were below the normal range in 14 of 20 (70%) patients, while it fell within the lower third in the remaining six patients. FSH levels were above the normal range in four patients, suggesting damage to spermatogenesis. LH levels were mildly increased in only three patients (15%). There was no significant difference in the gonadotrophin levels between patients with low or low-normal testosterone levels (Table IV). Nine men (47%) were referred with reduced libido and six (30%) had erectile dysfunction. By logistic regression, there was no direct correlation between testosterone levels and sexual dysfunction.

The female HPG axis after RT (Table V)

Ten women (50%) had menstrual disturbances; six of them suffered from amenorrhea. Recovery of menses occurred after 6, 10 and 24 months in three women, while no cycles occurred in the other three female patients up to study entry. Two women had transient polymenorrhea immediately after trans-
plant, with unknown endocrine pattern at that time. Another woman developed polymenorrhea during acetylsalicylic acid treatment, which required drug withdrawal.

Scattered levels of FSH, LH and E2 values were found in the patients compared with controls: however, their average values were similar in the two groups. Four women (20%) had FSH and LH values in the menopausal range with very low E2 levels. Their gonadotrophins were significantly higher and E2 lower than in patients with regular cycles (P < 0.001) (Table IV), while serum androgens were similar in both groups (data not shown). Three of these women suffered from persistent amenorrhea and one from oligomenorrhea; diagnosis of premature ovarian failure (POF) was made in all of them. The onset of menstrual disorders was subsequent to RT, and these women had not undergone any previous investigation of their HPG axis status. Another woman had a mild prolactin increase (28 ng/ml) and oligomenorrhea post-RT. Serum prolactin levels were higher in the female patients than in controls (P < 0.05), and were above the normal range in four cases (20%). None of the women suffered from galactorrhea. Testosterone (P < 0.05) and DHEA-S (P < 0.001) levels were significantly lower in the female patients than in controls, while androstenedione and 17-OHP were similar. Despite the evidence of low normal androgen levels, hirsutism was detected in six of the patients (30%), all receiving CsA treatment. Hypertrichosis was found in another five patients (25%).

**Ultrasound evaluation**

At ultrasound examination, testicular volume was reduced in the patients compared with controls (P < 0.001; Table II) and was significantly lower in patients with testosterone levels below the normal range (P < 0.05) (Table IV). Also, prostate volume was lower in patients than controls (P < 0.001; Table III). The ultrasound pattern of both organs was homogeneous and regular in all male patients, without any focal lesion. Prostate but not testicular volume correlated with serum testosterone levels (r = 0.67; P = 0.04).

In three female patients, simple ovarian cysts were found with a diameter of 2.5–4.5 cm. Patients with ovarian cysts at study entry had higher E2 values than the remaining patients and controls (P < 0.05) (Tables IV and V), suggesting functioning cysts. In the three women with POF, a decreased ovarian size was found (volume 1.6–3 cm3; P < 0.05). The ovarian volume of the remaining women was similar to that of controls (Tables IV and V).

**Gonadal status abnormalities versus gender, renal function and treatments**

Disorders of HPG axis function were similarly frequent in men and women (69 versus 50%; P = NS), when all abnormalities were considered. Inhibition of the reproductive axis was the most frequent finding in men, while in women disorders were variable even if most patients had menstrual alterations during the post-transplant period. Interestingly, increased prolactin levels occurred only in women (20% of women versus 0% of men).

### Table V. Hypothalamus–pituitary–ovarian axis evaluation in women (median and range)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 20)</th>
<th>Controls (n = 40)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH 6</td>
<td>4.2 (1.1–164)</td>
<td>2.65 (0.3–10)</td>
<td>2–13 IU/l</td>
</tr>
<tr>
<td>LH 6</td>
<td>6.2 (0.6–110)</td>
<td>4.2 (0.5–12)</td>
<td>2–15 IU/l</td>
</tr>
<tr>
<td>Prolactin 6</td>
<td>16 (4.8–75)a</td>
<td>12.5 (8–17.3)</td>
<td>5–20 mg/l</td>
</tr>
<tr>
<td>17β-estradiol 6</td>
<td>360 (36.7–1461)</td>
<td>227.6 (128.5–323)</td>
<td>120–734 pmol/l</td>
</tr>
<tr>
<td>17-OHP 6</td>
<td>3.6 (1.2–5.7)</td>
<td>2.1 (0.9–5.1)</td>
<td>0.3–6.0 nmol/l</td>
</tr>
<tr>
<td>Androstenedione 6</td>
<td>3.8 (0.7–8.73)</td>
<td>4.9 (3.1–7.3)</td>
<td>3.5–10.1 nmol/l</td>
</tr>
<tr>
<td>Testosterone 6</td>
<td>0.5 (0.34–0.7)b</td>
<td>1.4 (0.7–3.1)</td>
<td>0.7–3.47 nmol/l</td>
</tr>
<tr>
<td>DHEA-S 6</td>
<td>0.84 (0.5–1.7)b</td>
<td>6.5 (2.85–12.3)</td>
<td>2.2–11.3 µmol/l</td>
</tr>
<tr>
<td>Ovarian volume (cm3) 6</td>
<td>7.5 (1.5–9)</td>
<td>8.1 (6–10.1)</td>
<td>5.7–10 cm3c</td>
</tr>
</tbody>
</table>

*P < 0.05 and b P < 0.01 versus controls. according to Flaws et al., 2000 and Pavlik et al., 2001.

<sup>c</sup>Data relative to the follicular phase of the menstrual cycle.

Male patients with a GFR < 85 ml/min had significantly lower circulating testosterone levels (2.7 ± 1.1 versus 7.3 ± 1.6 ng/ml; P < 0.0001) than those with a higher GFR. In female patients, there were no differences regarding kidney function. Age and duration of the dialysis period did not modify the HPG axis as no direct linear correlation was found between these variables and gonadotrophins, prolactin, male testosterone and female E2 values (data not shown).

Subtle differences were found in men according to immunosuppressive treatments, but due to the small number of cases a detailed analysis of the effect of single immunosuppressive agent was not performed. Patients treated with >6 mg of MPD daily had DHEA-S levels significantly lower than those treated with lower doses (0.85 ± 0.5 versus 1.04 ± 0.75 µmol/l; P = 0.015), but no difference was found in testosterone levels, gonadotrophin levels and prostate volume. Testosterone levels were significantly lower in men treated with calcineurine inhibitors (CsA and/or TAC) (10.4 ± 3.1 versus 15.6 ± 3.5 nmol/l; P = 0.003) than in those not in this treatment category.

The 18 patients treated with AZA and/or MMF had significantly higher prolactin levels than patients not on this treatment (median 11.5 versus 7.4 µg/l, P < 0.01).

### Discussion

Abnormalities in the HPG axis function were frequent, being observed in 69% of men and 50% of women, and persisted long after successful RT.

Previously, several studies reported on gonadal status in RT recipients, with controversial results. While HPG axis alterations in men with end-stage renal disease are well known, being characterized by low testosterone and gonadotrophin levels, high serum prolactin and E2 values (Palmer, 1999), discordant data exist on male gonadal function in RT recipients. Adequate recovery of sexual and reproductive function was revealed in most patients on conventional immunosuppression studied 1–10 years after RT by De Celis and Pedron-Nuevo (1999). Normalization of E2, prolactin and testosterone values within 12 months after RT was also
reported in patients on CsA therapy (Samojlik et al., 1992). Conversely, only a partial improvement of gonadotrophin levels and spermatogenesis was reported early after RT in some studies (Prem et al., 1996; Akbari et al., 2003), while other authors have found persistent abnormalities of the HPG axis function in patients with functioning RT (De Besi et al., 1988; Nieszporek et al., 1990; Talbot et al., 1990; Chan et al., 1992).

We found a persistently inhibited HPG axis in most male patients: this was not related to alterations in E2 and prolactin production, as these hormone levels were within the normal range in all of them. Increased prolactin levels have been reported previously in transplanted men by some (Exaire et al., 1982) but not all (De Besi et al., 1988; Samojlik et al., 1992; Peces et al., 1994) authors. We have found increased 17-OHP levels in our patients, more in males than females, suggesting a possible negative influence of immunosuppressive treatments on the steroidogenic pathway. In fact, all patients were on glucocorticoids that are known to suppress GnRH release, consequently inhibiting all the HPG axis function (MacAdams et al., 1986). The adrenal source of androgens is also inhibited by glucocorticoids. Moreover, CsA has been shown to reduce testosterone production in vitro (Seethalakshmi et al., 1992) and to cause testicular damage in treated rodents (Srinivas et al., 1998). In humans, CsA whole blood levels have been inversely correlated with sperm concentration and motility (Eid et al., 1996). In our experience, calcineurin inhibitors showed a greater influence on testosterone secretion than MMF and AZA, without any further difference between CsA and TAC. However, the series of patients included in this pilot study is not large enough to draw final conclusions concerning single agents and their different dosage. No relationship was found between sexual function and type of immunosuppressive treatment by other authors (Handelsman et al., 1984; Ramirez et al., 1991; Peces et al., 1994; Rodriguez-Rodriguez et al., 1996).

A trend toward increased testosterone levels after RT suggests potential delayed improvement of testicular function, even if immunosuppressive treatments are maintained. A higher GFR indicating better allograft function was also associated with higher serum testosterone levels. Similarly, Handelsman et al. (1982) found that renal allograft function rather than different immunosuppression (CSA versus MPD + AZA) was the major determinant of gonadal function in 24 men. On the other hand, no relationship was found between endocrine disorders, age and period of uraemia.

Concerning sexual dysfunction, decrease of libido (47%) was reported more frequently than erectile dysfunction (30%) by our cohort of patients. However, with data on erectile dysfunction being self-reported by the patients, its actual prevalence may be higher. As there was no direct correlation between decreased libido, erectile dysfunction and circulating testosterone levels, some variable individual sensibility of sexual function to the testosterone production decrease can also be hypothesized. On the other hand, decreased sexual function can also be related to some psychological factors in subjects after organ transplant. Rodriguez-Rodriguez et al. (1996) found decreased libido in one-third (30%) and erectile dysfunction in about a half (45%) of 98 RT recipients. In patients with chronic renal failure, sexual dysfunction was found as frequently as in 80% (Palmer et al., 1999). As an organic component of this disorder has been demonstrated by abnormal nocturnal penile tumescence (Holdsworth et al., 1978), erectile dysfunction can be only partly reversible after RT. Finally, reduced prostate volume mirrored the reduction in testicular function as documented by a direct correlation with circulating testosterone values.

The HPG axis function in women is less clear than in men, either before or after RT. In chronic renal failure, menstrual disorders with an abnormal cyclic gonadotrophin regulation due to a hypothalamic defect were reported, while ovarian responsiveness to gonadotrophin stimulation is present. Therefore, ovarian function, although preserved, is mostly dysregulated with anovulatory cycles, low E2 and high prolactin values (Phocal et al., 1992; Palmer, 1999).

In our cohort of female RT recipients, abnormalities in menstrual cycles were frequent, being mostly transient; nevertheless, POF occurred in 20% of women. Similarly, anovulatory cycles with an increase in gonadotropin levels were described in ~20% of patients by Pietrzak et al. (1994), while 85% of female patients in pubertal stage IV–V reinitiated their menses between 1 and 8 months after RT in a study by Ferraris et al. (1987) with preserved gonadotrophin response to GnRH test in all four girls who had been investigated after RT. POF onset after RT does not seem to be caused by chronic renal failure prior to RT, as uraemia itself influences the HPG axis but does not cause the end-organ failure (Lim et al., 1980). Nevertheless, uraemia can increase cytokine generation, and contact with plasticizers in dialysis tubing may promote autoimmune disorders, that are quite a common finding in patients with chronic renal disease (Ali et al., 2000; Andreini et al., 2000). Alterations of the immune system function typical in the post-transplant period can contribute further to POF generation. However, it is difficult to demonstrate the autoimmune aetiology of POF, since the presence of organ-specific autoantibodies is often time-limited or only local (Hoek et al., 1997). Patients with ovarian cysts at study entry had higher E2 values than the remaining patients and controls. No relationship was found between female reproductive disorders, immunosuppressive treatments, age, period of uraemia and time from transplant. Also, no difference was found by Handelsman et al. (1984) in the endocrine pattern of 24 females treated by CsA or AZA + MPD. Excessive hair growth was found by the same authors in both treatment groups (Handelsman et al., 1984). Hirsutism also occurred in our female patients, despite showing low to normal androgen values, and regardless of the treatment employed, although this was more severe in women on CsA therapy. Prolactin levels were increased in 20% of women but not in men; however, physiologically, women have higher prolactin levels than men and the prevalence of hyperprolactinaemia is higher in women than in men (Colao et al., 2003). Whether this gender difference in prolactin secretion is also present in other pathological conditions such as during chronic renal failure and after RT is not known. However, it does not seem to depend on renal function, as higher prolactin levels were only found in women with creatinine levels similar to men.
Moreover, prolactin levels were lower in patients treated with calcineurin inhibitors, in line with previous evidence on a potent inhibitory effect of this class of drugs on the human prolactin gene (Nagai et al., 1996).

The major limit of this study is its small sample size, and this could have caused a lack of some possible influencing factors besides those we showed with an effect on the HPG axis function. However, our findings indicate that the alterations of the HPG axis are not simply a residual problem from the period of end-stage renal disease, but they are likely to be the consequence of a new post-transplant situation. Post-transplant dysregulation of the immune system and immunosuppressive treatments probably play an important role in the onset and maintenance of reproductive dysfunction following RT, in analogy with our previous results in patients after bone marrow transplant (Tauchmanová et al., 2002, 2003).

Interestingly, women with menstrual disturbances and amenorrhea underestimated their problems and did not ask for medical attention for their symptoms until study entry. In light of this, the function of the HPG axis should be evaluated in all patients after successful RT and abnormalities should be corrected by appropriate replacement therapies, as frequent reproductive function disorders may negatively influence general health and can contribute to further complications such as bone loss and cardiovascular diseases. Hormone replacement treatments require special medical surveillance in transplanted patients, as interaction between exogenous hormones and immunosuppressive therapy can occur at numerous levels (Ali et al., 2000). Furthermore, the presence of ovarian cysts requires endocrine and ultrasonographic follow-up, as the patients with end-stage renal disease (Maisonneuve et al., 1999) and those on immunosuppression (Lutz and Heemann, 2003) are at increased risk of malignancies.

In conclusion, a high prevalence of HPG axis abnormalities is demonstrated in RT recipients with well-functioning allografts. Alteration of the HPG axis is probably multifactorial, being influenced prevalently by immunosuppressive treatments in men with further influence by allograft function and time elapsed from transplant. In women, more variable disorders suggest some individual factors influencing the HPG axis with less inhibitory effects of immunosuppression. Other mechanisms are likely to be responsible for reproductive abnormalities, especially in women, and the apparently gender-related differences remain to be clarified.

References


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