Division of Endocrinology, Department of Medicine, Department of Pathology¹) and Department of Gynecology and Obstetrics²), University of Nijmegen, Nijmegen, The Netherlands

FERTILE EUNUCH SYNDROME VERSUS CLASSIC HYPOGONADOTROPHIC HYPOGONADISM

By

A. G. H. Smals, P. W. C. Kloppenborg, U. J. G. van Haelst¹), R. Lequin²) and T. J. Benraad

ABSTRACT

The functioning of the hypothalamo-pituitary-target organs axis was assessed in 3 patients with 'fertile eunuch' syndrome (FE) and 6 patients with 'classic' hypogonadotrophic hypogonadism (HH) with or without hyposmia. Both groups of patients did not differ from each other with regard to basal serum prolactin levels, pituitary growth hormone and thyrotrophin reserve and the thyroid or adrenal gland function. Both groups differed, however, with respect to the hypothalamo-pituitary-gonadal function: 1. the pituitary LH response to exogenous LH-RH was (low)-normal in FE and blunted in HH; 2. the basal FSH levels were normal in FE and undetectable in HH; 3. the basal LH levels were normal in FE and 3/6 patients with HH and low in the remaining three; 4. the basal and HCG stimulated plasma testosterone concentrations were significantly higher in FE than HH. The data suggest that FE represents a less severe form of LH-RH deficiency, rather than a distinct disorder.

Pasqualini & Bur (1950) described a patient with eunuchoidism and normal sized testes, preserved spermatogenesis with virtual absence of mature Leydig cells and clinically and biochemically a normal androgenic response to HCG administraton. Hitherto about 50 patients have been reported in literature. This syndrome for which the term 'fertile eunuch' syndrome was coined by McCullagh & Beck (1952) and McCullagh et al. (1953) has been thought to

Requests for reprints should be sent to A. G. H. Smals, Division of Endocrinology, Department of Medicine, University of Nijmegen, Nijmegen, The Netherlands.

389
originated in a primary pituitary deficiency of LH release, with a consequent lack of trophic and secretory stimulation of Leydig cells in the presence of normal FSH secretion (Pasqualini & Bur 1950; McCullagh & Beck 1952; McCullagh et al. 1953; Pasqualini & Bur 1955; Faiman et al. 1968). Recent reports, however, point to a deficient release of hypothalamic gonadotrophin releasing hormone as the primary anatomical or functional defect leading to LH deficiency, rather than to the pituitary gland (Bonati et al. 1974; Hornstein et al. 1974; del Pozo et al. 1975; Williams et al. 1975; Boyar et al. 1976). This finding, however, interferes with the duality theory of the gonadotrophin releasing hormone system unless it is assumed that the hypothalamic releasing hormone produced is itself defective leading to stimulation of FSH and not of LH (Williams et al. 1975). However, LH deficiency is not invariably present in these patients with fertile eunuchoidism as normal LH levels have been reported in this syndrome (vide infra). In view of these conflicting reports it seemed worthwhile to report on the hormonal studies in 3 patients with fertile eunuch syndrome (FE) in comparison to the data in 6 patients with ‘classic’ hypogonadotrophic hypogonadism (HH) with or without anosmia.

CASE REPORTS

Patient 1, a 27 year old man was seen at the endocrine clinic in 1974 for evaluation of his delayed sexual maturation, weak libido and absence of ejaculations. Physical examination revealed a eunuchoid man (height 179 cm, span 188 cm) with a high pitched voice, scanty axillary and pubic hair, absent beard and moustache growth and a small phallus (length 4 cm). The testes measured 4 x 3.5 cm and were of normal consistency. Olfaction (Henkin & Bartter 1966) and the karyotype [46,XY] were normal. A testicular biopsy revealed about 300 seminiferous tubules with maturation of the germ cells to spermatids and spermatozoa. Leydig cells were greatly reduced in number (Fig. 1). On the strength of the clinical histological and hormonal (vide infra) evidence a diagnosis of ‘fertile eunuchoidism’ was made and the patient was treated with HCG (Pregnyl®, Organon 3 x 1500 U weekly) resulting in increased masculinization and the ability to ejaculate (semen analysis 11 x 10^6 spermatozoa/ml).

Patient 2, a 36 year old man was referred to the endocrine clinic in 1975 because of poor libido, defective sexual intercourse, scanty beard growth and lacking ejaculations. Physical examination revealed a man with high pitched voice, gynaecomastia, normal body proportions (height 174 cm, span 177 cm, upper body/lower body ratio 89/85), scanty axillary and pubic hair, absent beard growth and feminine fat distribution. The phallus was small (4.5 cm), both testes were normal, 3.5 x 2.5 cm. Olfaction and a sella tomogram were normal. The karyotype was 46,XY).

A testicular biopsy showed 100 seminiferous tubules with all stages of germ cell maturation. Leydig cells were atrophic and reduced in number. Fertile eunuchoidism was considered on the base of clinical, histological and hormonal (vide infra) findings and the patient was treated with HCG (Pregnyl®, Organon 3 x 1500 U, 3 weekly) resulting in increased masculinization and the ability to ejaculate (semen analysis 2.5 x 10^6 spermatozoa/ml).
Patient 3, a 20 year old man was referred in 1976 because of deficient secondary sex characteristics and absent ejaculations. Previous history revealed parotitis without complicating orchitis.

At physical examination the patient was eunuchoid (height 167 cm, span 180 cm, upper/lower body ratio 81/86) with a high pitched voice, scarce pubic hair and without any beard or axillary hair growth. The phallus was small (4.5 cm), the testes measured 3.6 × 2.4 cm (left) and 3.6 × 2.2 cm (right). A sella planigram was normal, the karyotype was 46,XY. A testicular biopsy revealed 60 normal seminiferous tubules with all stages of germ cell maturation including spermatozoa. Leydig cells were strongly reduced in number. Fertile eunuchoidism was considered and the patient was treated with HCG (Pregnyl®, Organon 3 × 1500 U/weekly), resulting in adequate virilization and the occurrence of nightly ejaculations 4 months after start of therapy.

Six patients with classic hypogonadotrophic hypogonadism (22 × 2 years) (karyotype 46,XY) were investigated, two had concomitant hyposmia (HH 2 and 3). All were
eunuchoid with absent heard growth, scant or absent pubic hair and axillary hair, a small phallus and small sized testes (1 × 1 cm). Cryptorchidism was present in one patient (HH 2) and gynecomastia in two of them (HH 5 and 6). A testicular biopsy in two of them revealed small sized seminiferous tubules with sporadic spermatogonia but completely absent spermatogenesis. Leydig cell were lacking in the interstitial spaces.

Ten eugonadal men with proven fertility (32.4 ± 9.7 years) served as control subjects.

METHODS

Plasma cortisol levels were measured according to the method of de Moor et al. (1960). Plasma testosterone was measured by a radioimmunoassay with a paper chromatographic purification step before the assay (Smals et al. 1976). Total serum thyroxine (T₄) levels were assayed by a modification of the Murphy-Jachan assay and serum T₃ levels by a direct radioimmunoassay (Smals et al. 1977). Serum TSH was determined by a heterologous radioimmunoassay (Smals et al. 1977), serum prolactin by a homologous radioimmunoassay (Hwang et al. 1971; Rolland et al. 1975). Growth hormone levels were determined by a homologous radioimmunoassay.

Insulin stimulated HGH release. – After an overnight fast 0.1 U/kg insulin was given iv and plasma samples obtained at 0, 10, 20, 30, 45, 60, 90 and 120 min for determination of glucose and growth hormone (HGH). The hypoglycaemic stimulus was considered adequate if the plasma glucose levels measured by auto-analyzer fell below 40 mg/100 ml.

TRH stimulation. – Blood samples for TSH assay were drawn from an indwelling venous catheter at times −15, 0, 10, 20, 30, 60, 90 and 120 min after iv bolus injection of 200 μg TRH (Roche). Blood samples for T₃ and T₄ assay were collected at times −15, 0 and 120 min.

LH-RH stimulation. – Blood samples for serum LH and FSH determination were drawn from an indwelling catheter at times −15, 0, 10, 20, 30, 60, 90 and 120 min after iv injection of 100 μg of LH-RH (Hoechst).

Testosterone response to HCG. – Plasma testosterone was determined before and after short term (1500 U daily for 3 days) and long term 1500 U, 3 times weekly for 3 weeks) HCG (Pregnyl®, Organon) administration.

Statistical analysis was performed using the Mann and Whitney U test.

RESULTS

Serum prolactin levels were normal in patients with FE and HH tested. Insulin induced hypoglycaemia elicited a subnormal HGH response in the only patient with FE and in 5 patients with HH tested.

Adrenal gland function was adequate in all patients. Plasma cortisol levels fell within the normal range and showed a normal diurnal rhythm in both the patients with FE and HH.

The pituitary-thyroid axis function was judged to be normal in the pa-
Table 1.
Laboratory data of 3 patients with 'fertile eunuch' syndrome (FE) and 6 patients with 'classic' hypogonadotrophic hypogonadism (HH).

<table>
<thead>
<tr>
<th></th>
<th>Insulin A HGH* (ng/ml)</th>
<th>Serum prolactin (ng/ml)</th>
<th>Serum TSH (μU/ml)</th>
<th>Serum T3 (ng/dl)</th>
<th>Serum T4 (μg/dl)</th>
<th>Plasma cortisol (μg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>TRH Δ max.</td>
<td>Basal</td>
<td>TRH Δ 2 h</td>
<td>Basal</td>
<td>TRH Δ 2 h</td>
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<tr>
<td>Controls</td>
<td>&gt; 10</td>
<td>&lt; 10</td>
<td>&lt; 2–10</td>
<td>7.0–18.6</td>
<td>85–180</td>
<td>&gt; 17</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pat. 1</td>
<td>8.0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>–</td>
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<td>9.5</td>
<td>6.5</td>
<td>106</td>
<td>32</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
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<td>2.8</td>
<td>4.0</td>
<td>8.0</td>
<td>10.1</td>
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<td>–</td>
</tr>
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<td>7.0</td>
<td>5.5</td>
<td>5.5</td>
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<td>2.5</td>
<td>4.6</td>
<td>10.0</td>
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<td>81</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>135</td>
<td>–</td>
</tr>
</tbody>
</table>

* Insulin induced maximal growth hormone increase.
Table 2.
The hypothalamo-pituitary-gonadal axis in 3 patients with 'fertile eunuch' syndrome (FE) and 6 patients with 'classic' hypogonadotrophic hypogonadism (HH).

<table>
<thead>
<tr>
<th></th>
<th>Serum LH (mIU/ml)</th>
<th>Serum FSH (mIU/ml)</th>
<th>Plasma testosterone (ng/dl)</th>
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</thead>
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<td>Basal</td>
</tr>
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<td>27–160</td>
<td>0.6–11.2</td>
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<tr>
<td>'FE' syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pat. 1</td>
<td>8.0</td>
<td>–</td>
<td>1.2</td>
</tr>
<tr>
<td>2</td>
<td>10.9</td>
<td>31</td>
<td>1.1</td>
</tr>
<tr>
<td>3</td>
<td>10.0</td>
<td>34</td>
<td>0.9</td>
</tr>
<tr>
<td>'Classic' HH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pat. 1</td>
<td>7.6</td>
<td>5.3</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td>2</td>
<td>8.1</td>
<td>4.6</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td>3</td>
<td>5.8</td>
<td>13.2</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td>4</td>
<td>3.8</td>
<td>7.2</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td>5</td>
<td>5.9</td>
<td>–</td>
<td>&lt; 0.6</td>
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<tr>
<td>6</td>
<td>11.0</td>
<td>–</td>
<td>&lt; 0.6</td>
</tr>
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</table>
patients with FE and HH on the base of normal basal serum $T_3$, $T_4$ and TSH levels. The pituitary TSH response to TRH administration was blunted in one of the patients with FE (patient 2) and 2 of the patients with HH (patient HH 2 and 4). All patients with FE and HH tested showed normal serum $T_3$ responses to TRH administration.

Basal serum FSH levels were in the lower normal range in the patients with FE, but undetectable in the patients with HH. Basal serum LH levels were low normal in the patients with FE, subnormal in three patients with HH and low normal in the remaining three. Short term intravenous LH-RH administration elicited a low normal LH response in two patients with FE, but a low or subnormal LH increase in 4 patients with HH tested. The FSH response to LH-RH administration was normal in all patients with either FE or HH.

The mean basal plasma testosterone level in the patients with FE (68 ± 13 ng/10 ml) was significantly higher ($P < 0.01$) than the mean value in the patients with HH (36 ± 14 ng/100 ml). The plasma testosterone response to short and long term HCG administration was also significantly higher in the patients with FE (309 ± 147 and 958 ± 336 ng/100 ml respectively) than in the patients with HH (80 ± 87 and 323 ± 91 ng/100 ml respectively) ($P < 0.05$).

**DISCUSSION**

The three patients with FE in this report all fulfilled the criteria of the ‘fertile eunuch’ (FE) syndrome, 1) evidence of hypoandrogenism despite normal sized testes; 2) the presence of variable degrees of active spermatogenesis in a representative number of seminiferous tubules studied, in the absence of mature Leydig cells and 3) clinical and chemical evidence of increased androgenicity in response to exogenous HCG, indicating the presence of HCG-sensitive Leydig cells and androgen sensitive peripheral target cells. The patients with classic hypogonadotrophic hypogonadism (HH) with or without concomitant hyposmia showed evidence of androgen deficiency in the presence of small testes with atrophy of the seminiferous tubules and absent spermatogenesis. The two groups of patients did not differ in their pituitary growth hormone reserve and adrenal or thyroid gland functions. Prolactin levels were normal in all patients. Pituitary TSH reserve was impaired in one patient with FE and two of the patients with HH, but the $T_3$ response to exogenous TRH was normal in all patients tested. Taken together these data do not point to a basic difference in the function of the pituitary gland between patients with FE and HH. The blunted growth hormone response observed in both groups may be the consequence of androgen deficiency (*Illig & Prader 1970; Penny & Blizzard 1972*) and has also been reported by others (*Boyar et al. 1973*).
Both groups of FE and HH patients differed, however, from each other in the functioning of their hypothalamic-pituitary-gonadal axis, 1) the pituitary LH reserve was (low)-normal in FE, but blunted in HH, 2) the basal FSH levels were low normal in FE, but undetectable in HH, 3) the basal and HCG stimulated plasma testosterone concentrations were higher in FE than in HH. Thus both syndromes differ at least quantitatively. It is stressed that in the patients with FE of this study basal LH levels were in the normal range as in half of the patients with HH. The latter finding is in agreement with data of Boyar et al. (1973) and Santen & Paulsen (1973) who also reported occasionally normal LH values in patients with gonadotrophin deficiency.

Normal pituitary LH reserve in FE has been reported in recent literature (Bonati et al. 1974; Hornstein et al. 1974; del Pozo et al. 1975; Williams et al. 1975; Boyar et al. 1976) as in the present study. In patients with HH the gonadotrophin response to LH-RH administration has been found to be rather heterogeneous in that some subjects show no response and the response of others is relatively low or (sub) normal (Roth et al. 1972; Bell et al. 1973; Zarate et al. 1973; Coscia et al. 1974; Reiter et al. 1976; Mortimer et al. 1976; Boyar et al. 1976). Basal serum FSH levels were normal in the patients with FE from the present study, which is in agreement with data of most other authors (Pasqualini & Bur 1950, 1955; McCullagh & Beck 1952; McCullagh et al. 1953; Faiman et al. 1968; Bonati et al. 1974; Hornstein et al. 1974; del Pozo et al. 1975; Williams et al. 1975; Santen & Paulsen 1973; Kjessler 1972). Prior to 1968 lack of circulating LH in the presence of normal FSH levels has been described as characteristics for the syndrome of FE (Pasqualini & Bur 1950, 1955; McCullagh & Beck 1952; McCullagh et al. 1953; Faiman et al. 1968). In more recent literature, however, circulating plasma LH levels in FE have been reported to be low normal or even normal (Kjessler 1972; Santen & Paulsen 1973; Boyar et al. 1973, 1976; Bonati et al. 1974; Hornstein et al. 1974; del Pozo et al. 1975; Williams et al. 1975).

Moreover also in urinary extracts bioassayable and immunoassayable LH level have been found to be (low) normal in this syndrome (Christiansen 1972). Therefore it seems unlikely that isolated LH deficiency is the underlying cause of this disorder as stated in older literature.

The most striking differences found between patients with FE and HH are the normal sized testes and virtually complete spermatogenesis in the former. The existence of virtually complete spermatogenesis in severely hypoandro-genic men with FE seems paradoxical. Indeed the presence of sufficient amounts of FSH, LH and testosterone is considered prerequisite for normal androgenicity and spermatogenesis (Sanborn et al. 1976; Lostroh 1976).

Basal plasma testosterone levels differed significantly between the two groups of eunuchoid patients of this study, the values being significantly higher in the patients with FE than in the patients with HH, a finding in agreement
with very recent data of Boyar et al. (1976). In literature basal plasma testosterone levels in FE have been reported to vary widely from slightly lowered to definitely low values (Kjessler 1972; Santen & Paulsen 1973; Boyar et al. 1973, 1976; Bonati et al. 1974; del Pozo et al. 1975; Williams et al. 1975). However, the mean plasma testosterone value in 14 patients with FE collected from literature, and the present study (93 ± 61 ng/100 ml) was significantly (P<0.01) higher than the mean value in 21 patients with ‘classic’ HH (45 ± 35 ng/100 ml) collected from reports of the same investigators. Short and long term HCG administration elicited a higher testosterone response in the patients with FE than in the patients with HH of the present study. A possible explanation for the higher testosterone response in the patients with FE might be the presence of FSH which has been reported to potentiate the effect of LH on the Leydig cells (Odell & Swerdloff 1973; Lostroh 1969, 1976; Bartke et al. 1975).

Apart from potentiating the effect of LH in promoting testosterone synthesis, FSH has been reported to play a specific role in the regulation of androgen levels in the immediate vicinity of dividing and differentiating germ cells (Bartke et al. 1975). FSH stimulates the uptake of testosterone by rat seminiferous tubules, binds to Sertoli cell receptors (Means & Vaitukaitis 1972) and increases the synthesis of testicular androgen binding protein (ABP) by the Sertoli-cells (Hansson et al. 1973, 1975) facilitating the transfer of androgens to their specific cytoplasmatic receptor in the germ cells (Sanborn et al. 1976). Furthermore FSH increases testicular testosterone concentration in hypophysectomized Sertoli-cell enriched rats (Means et al. 1976). In rams FSH in combination with LH has been demonstrated to cause a greater increase of testosterone and dihydrotestosterone in rete testis fluid (not in plasma) than LH alone (Bartke et al. 1975). It might therefore be conceivable that the LH and testosterone present in FE patients synergistically with FSH can provide sufficiently high androgenic steroid concentrations in the seminiferous tubules to sustain spermatogenesis whereas circulating plasma testosterone in FE, though higher than in HH is still insufficient to induce a normal virilisation. In this theory the absent spermatogenesis in HH could be conceived as the expression of the absence of circulating FSH together with significantly lower circulating testosterone levels.

The data in this study do not allow us to consider the differences between the two groups of eunuchoid patients to be the expression of a fundamental difference in hypothalamo-hypophyseal interrelations. Very recently Boyar et al. (1976) demonstrated pubertal sleep-related patterns of circulating LH and testosterone to be more mature in FE than in HH and they therefore reasoned FE syndrome to represent a less severe deficiency of LH-RH rather than a distinct disorder. The data presented in this paper seem to support this thesis.
REFERENCES


398


Received on May 5th, 1977.