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erinary Gonadotrophins in the Sertoli-Cell-Only Syndrome

By

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Abstract

In order to study the hypophyseal-testicular axis in males with complete absence of germinal epithelium, the urinary total hypophyseal gonadotrophins (HG), urinary follicle stimulating hormone (FSH) and urinary luteinizing hormone (LH) were measured by specific bioassays in 12 males with classical Sertoli-cell-only syndrome and compared with HG, FSH and LH in normal and castrated men. HG and FSH were significantly higher than HG and FSH in normal men \( (P < 0.0025, P < 0.0005, \text{ respectively}) \), but significantly lower than in castrated men \( (P < 0.001, P < 0.01, \text{ respectively}) \). LH was not different from LH of normal men, but significantly lower than in castrated men \( (P < 0.0005) \). All patients had normal excretion of androgen metabolites (androstosterone + aetiocholanolone) but a dexamethasone suppression test, performed in 8 subjects, revealed that in 2 cases of testicular origin, the values were below the normal range. The excretion of oestrogens was within the normal range.

The presented data support the concept that the germinal epithelium produces a substance capable of inhibiting FSH secretion from the hypophyses, the Sertoli cell itself, however, having a basal production of this inhibitor. The finding of low excretion of testicular androgen metabolites in some of the patients and normal urinary LH, indicates that disturbances in the LH – testosterone feedback mechanism in such patients may occur and that the previous concept of isolated defects of spermatogenesis in all such patients was erroneous.

Del Castillo et al. (1947) described a syndrome produced by absence of the germinal epithelium without impairment of the Sertoli or Leydig cells, later called the Sertoli-cell-only syndrome or del Castillo's syndrome. This syndrome
was different from that described earlier by Klinefelter et al. (1942) in which both the germinal cells and the Sertoli cells were involved in the pathological process. In the 5 patients published by del Castillo et al. (1947) the urinary FSH was within the normal range in all cases and accordingly they concluded that the Sertoli cells produced a substance capable of inhibiting FSH secretion from the pituitary gland. Later Howard et al. (1950) found moderately increased urinary FSH in patients with the Sertoli-cell-only syndrome and suggested that the substance capable of inhibiting the secretion of FSH was produced by the germ cells and that there was a lack of this substance in the Sertoli-cell-only syndrome. Recent reports of FSH and LH in males with impaired spermatogenesis have been conflicting (Paulsen 1968; Rosen & Weintraub 1971; Christiansen 1971; Franchimont et al. 1972; Leonard et al. 1972; de Kretser et al. 1972; Mauss & Börsch 1973) and the reports of Wide & Kjessler (1969) and Kjessler & Wide (1973) who found moderate elevated LH in oligospermic males raises the question whether the Leydig cell functions normally in such patients.

On this background we found it of interest to study urinary gonadotrophins and Leydig cell function in a group of males with the Sertoli-cell-only syndrome.

MATERIAL AND METHODS

Patients

Twelve males aged 25–39 years, mean 29.8 years were referred by practitioners to the Male Hypogonadism Study Section, University Hospital of Copenhagen for infertility. They underwent standard physical examinations including measurement of the testes volume by the orchidometer (Prader 1966). The excretion of gonadotrophins (cf. below), oestrogens (Brown et al. 1968), androgen metabolites (Johnsen 1956) and 17-KGS was determined. In 8 of the patients a dexamethasone suppression test (DXM), in 6 cases combined with human chorionic gonadotrophin stimulation (DXM-HCG) in order to study the reserve capacity of the Leydig cells was made (Johnsen et al. 1971). The excretion of androsterone (A) and aetiocholanolone (Ae) was measured by the method of Johnsen (1956). Mean normal values for A + Ae for men of 20-40 years are 8.7 mg/day (95% limits 4.8–15.7), during DXM 4.2 mg/day (95% limits 2.2–8.3) and the rise during DXM-HCG 5.0 mg/day (95% limits 1.9–12.9) (Johnsen et al. 1971). The body hair was assessed and recorded in classes from 0–6, class 0 being absence of hair and class 6 being normal adult amounts of hair with a normal male distribution. Spcrm counts were performed by Dr. R. Hammen according to methods previously described (Hammen 1944). Evaluation of spermatogenesis was performed by the testicular biopsy score count method (Johnsen 1970). Each tubular section in one biopsy section is given a score from 10–1, score 10 being full spermatogenesis, normal germinal epithelium and score 1 being no cells in the tubular section. Anything less than step 10 is essentially inferior as tubules below this step contribute little to fertility and below step 8 not at all. In order to calculate a mean score (MS) the number of tubules recorded for each score is multiplied by that score and the sum of all 10

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multiplications is divided by the total number of tubules. Normal values for MS are 9.38 ± 0.24. In the Sertoli-cell-only syndrome MS is 2.0 ± 0.03 (cf. Johnsen 1970). For further details of this method the reader is referred to the paper cited.

The degree of hyalinization of the tubules was judged and recorded by a hyaline score (HS) from 1 to 6, HS 1 being no hyalinization at all, HS 2 = minimal changes, HS 3 = small amounts in all or much in few tubules, HS 4 and 5 = a lot in all tubules and HS 6 = total hyalinization.

In addition the number of Leydig cells was assessed and recorded in a Leydig score (LS) from 1 to 6, LS 3 being normal amounts of Leydig cells, LS 1 absence of Leydig cells, LS 2 definitely decreased number, LS 4 slight to moderate hyperplasia, LS 5 pronounced hyperplasia and LS 6 maximal hyperplasia (= highest amounts ever seen in large series of testicular biopsies).

Furthermore the internal diameter of 10 cross-sectioned tubules was measured with an ocular micrometer and the mean diameter calculated. Normal values are 162–215 μm. All examinations of the testicular biopsies were performed by Dr. Svend G. Johnsen.

All the patients collected four to ten 24 h urine samples, which were extracted by the method of Johnsen (1958), pooled and divided into 2 portions for the determination of follicle stimulating hormone (FSH) and luteinizing hormone (LH). The analyses of urinary total hypophyseal gonadotrophins (HG) were performed before the FSH and LH analyses.

Controls

Twenty-eight normal men aged between 21 and 44 years, mean 31.2 years were used as controls. They were all healthy, had testes of normal size and consistency, were normally virile without any sign of endocrine disorder and those who were married and wanted children had proved their fertility by having at least one child. All the subjects collected twelve to fourteen 24 h urine samples which were extracted by the method of Johnsen (1958), pooled and divided into 3 portions for the 3 bioassays. In 7 of the controls no determination of HG was performed. The mean excretion of HG was 13 MUU/day (95% limits 3.2–52.8), of FSH 5.8 IU/day (95% limits 1.6–21.1) and of LH 6.3 IU/day (95% limits 2.4–16.1). The mean FSH/LH ratio was 0.93, the 95% limits being 0.33–2.63.

Castrated men

This group has been described in detail elsewhere (Christiansen 1973). It consists of 13 men, all castrated for legal reasons, aged between 23 and 56 years, mean 38.8 years. The time interval between castration and the investigation varied from 1 month to 24 years. The mean excretion of HG was 125 MUU/day (95% limits 33–476), of FSH 61 IU/day (95% limits 18–214) and of LH 22 IU/day (95% limits 8–59). The mean FSH/LH ratio was 2.8, the 95% limits being 1.0–7.6.

Bioassays

1. The urinary HG was measured by the mouse uterus test (Johnsen 1958, 1959) and expressed in mouse uterus units (MUU) per 24 h. One ampoule of the 2. International Reference Preparation for Human Menopausal Gonadotrophins (2. IRP-HMG) contains 40 IU FSH, 40 IU LH and 133 MUU.
Table 1.
Details of the 12 patients with Sertoli-cell-only syndrome.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Body hair*</th>
<th>Mean testes volume (ml)</th>
<th>Spermatozoa per ejaculate</th>
<th>Mean score*</th>
<th>Leydig cell score*</th>
<th>Hyaline score*</th>
<th>Mean tubular diameter (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>6</td>
<td>6</td>
<td>0</td>
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<td>115</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>6</td>
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<td>5</td>
<td>102</td>
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<tr>
<td>4</td>
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<td>6</td>
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<td>114</td>
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<td>98</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>6</td>
<td>10</td>
<td>0</td>
<td>2.0</td>
<td>5</td>
<td>1</td>
<td>135</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>6</td>
<td>8</td>
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<td>6</td>
<td>3</td>
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<td>5</td>
<td>5</td>
<td>140</td>
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</table>

* For explanation, see text.
2. The urinary FSH was measured by the rat ovarian augmentation test (Steelman & Pohley 1953) and performed as previously described (Christiansen 1972). The extracts were assayed against the 2. IRP-HMG with a 3+5 design expressing the activity in IU per 24 h. Five rats per dose.

3. The urinary LH was measured by the ventral prostate weight method in hypophysectomized rats (VPW) (Greep et al. 1941) and performed as previously described (Christiansen 1967). The extracts were assayed against the 2. IRP-HMG in a 2+2 design expressing the activity in IU per 24 h. Five to eight rats per dose. The bioassays were calculated according to a computer programme for bioassays (McArthur et al. 1966). Only statistically valid assays were accepted.

RESULTS

1. Comments on patients

The 12 patients are characterized in Table 1. All were normally virile, having normal libido and potency. None had a relevant history. All were chromatin-negative, none had gynaecomastia. The volume of the testes varied between 4 and 12 ml; however none had testes of normal size and none had very small testes as in Klinefelter's syndrome (1–2 ml). In all cases the consistency was soft. All had aspermia. The testicular biopsies revealed a MS of 2.0 (cf. Johnsen 1970) and a decreased mean tubular diameter. Normal amounts of Leydig cells were observed in 1 case, 2 had moderate hyperplasia, 7 pronounced hyperplasia and 2 maximal hyperplasia. Three patients had no hyalinization of the tubules, 7 moderate and 2 severe hyalinization. The excretion of androgen metabolites was normal (Table 2). A DXM-suppression test however, revealed that in 2 cases (7 and 8) those of testicular origin were below the normal range, but the mean did not differ significantly from that of normal men. A + Ae from the adrenals were below the normal range in case 10 and in the lower normal range in case 4, but the mean was not significantly different from that of normal men. The 6 patients in whom a DXM-HCG test was performed had normal response to HCG (Table 2) and thus showed normal reserve capacity of the Leydig cells. The excretion of oestrogens and dehydroepiandrosterone (DHA) was normal in all cases.

2. Results of bioassays

As the excretion of hypophyseal gonadotrophins shows a log-normal distribution, all values were transformed into logarithms in the statistical calculations and the log values are used throughout this study. All means are accordingly geometric means (anti-log of mean log values).

In the following 4 figures HG, FSH, LH and FSH/LH ratio of the Sertoli-cell-only syndrome are compared with those of normal and castrated men.
Table 2.
The excretion of follicle stimulating hormone (FSH), luteinizing hormone (LH) and androsterone (A) + aetiocholanolone (Ae) of testicular and adrenal origin, separated by a dexamethasone suppression test and the rise in A + Ae after stimulation with human chorionic gonadotrophin (HCG) in 12 men with the Sertoli-cell-only syndrome. Mean normal values are indicated below, the 95% limits in brackets.

<table>
<thead>
<tr>
<th>Case</th>
<th>FSH IU/day</th>
<th>LH IU/day</th>
<th>Androsterone + Aetiocholanolone mg/day</th>
<th>Rise after HCG stimulation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>total</td>
<td>testicular</td>
</tr>
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<td>3.7</td>
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<td>2</td>
<td>50</td>
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<td>8.1</td>
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<td>3</td>
<td>15</td>
<td>3</td>
<td>7.2</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
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<td>4.7</td>
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<td>39</td>
<td>10</td>
<td>7.0</td>
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<tr>
<td>6</td>
<td>42</td>
<td>15</td>
<td>6.8</td>
<td>–</td>
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<td>7</td>
<td>36</td>
<td>18</td>
<td>8.0</td>
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<td>8</td>
<td>13</td>
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<td>2.0</td>
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<td>11</td>
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<td>9.3</td>
<td>4.7</td>
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<tr>
<td>10</td>
<td>8</td>
<td>5</td>
<td>6.5</td>
<td>5.6</td>
</tr>
<tr>
<td>11</td>
<td>14</td>
<td>11</td>
<td>8.1</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>5</td>
<td>4.9</td>
<td>–</td>
</tr>
<tr>
<td>Normal men:</td>
<td></td>
<td></td>
<td>5.8</td>
<td>(1.6–21.1)</td>
</tr>
</tbody>
</table>
Urinary total hypophyseal gonadotrophins (HG) in 12 patients with the Sertoli-cell-only syndrome compared to HG of normal and castrated men. Logarithmic scale. Each point indicates 1 subject.

The means and 95% limits refer to the Sertoli-cell-only syndrome since the means and 95% limits of normal and castrated men have been mentioned above.

Fig. 1 shows HG of the 3 groups. HG of the Sertoli-cell-only syndrome is 2.5 times higher than the HG of normal men, the mean being 32 MUU/day (95% limits 8–129). This difference is statistically significant \( (t = 3.5, P < 0.0025) \). Compared to HG of castrated men however, the HG of the Sertoli-cell-only syndrome is significantly lower \( (t = 4.9, P < 0.001) \).
FSH is 3.5 times higher than FSH of normal men (Fig. 2), the mean being 21 IU/day (95% limits 6–76). This difference is statistically highly significant \( t = 5.8, P < 0.0005 \). Like HG, FSH of the Sertoli-cell-only syndrome is significantly lower than FSH of castrated men \( (t = 3.7, P < 0.01) \).

Fig. 3 shows the LH of the 3 groups. The mean LH of the Sertoli-cell-only syndrome is 8 IU/day (95% limits 3–21) which is not significantly different from that of normal men \( (t = 1.5, P < 0.10 > 0.05) \) but significantly lower than the LH of castrated men \( (t = 4.2, P < 0.001) \). Consequently the FSH/LH ratio of the Sertoli-cell-only syndrome is 2.8 times higher than that of normal men (Fig. 4). The mean is 2.6 (95% limits 0.9–7.4) and this difference is statistically significant \( (t = 5.7, P < 0.0005) \). The FSH/LH ratio is exactly the same as that found in castrated men (cf. above).

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**Fig. 2.**

Urinary follicle stimulating hormone (FSH) in 12 patients with the Sertoli-cell-only syndrome compared to FSH of normal and castrated men. Logarithmic scale. Each point indicates 1 subject.
Urinary luteinizing hormone (LH) in 12 patients with the Sertoli-cell-only syndrome compared to LH of normal and castrated men. Logarithmic scale.
Each point indicates 1 subject.

No correlation was found between HG, FSH and LH respectively on the one hand and the Leydig score, hyaline score, mean tubular diameter and the excretion of androgen metabolites on the other.

**DISCUSSION**

The characteristic clinical findings of the Sertoli-cell-only syndrome are: 1) a normally virile man without any sign of endocrine disorder, 2) bilateral small testes, about half normal size, 3) a past history negative for diseases which could have been harmful to the germinal epithelium, 4) sterility with aspermia, 5) a testicular biopsy showing small seminiferous tubules with complete absence of germinal epithelium, presence of normal Sertoli cells and Leydig cells.

Our patients fulfil the clinical criteria mentioned above, as all were normally virile without any sign of endocrine disorder except for case 12 who had slightly reduced growth of beard. None of the patients had a relevant history
and all were sterile with aspermia and bilateral small testes. The testicular biopsies showed decreased size of the tubules, no germ cells and Sertoli and Leydig cells of normal appearance. However only one patient had normal amounts of Leydig cells, in nine cases there was a pronounced hyperplasia, and this general Leydig cell hyperplasia was real and not merely a result of the small tubules.

Del Castillo et al. (1947) mentioned a sixth criterion for their syndrome: Normal urinary FSH and slightly reduced urinary 17 KS. However, Howard et al. (1950) found elevated FSH levels in the Sertoli-cell-only syndrome, but both investigators used semi-quantitative and unspecific methods for the determination of FSH. Recently de Kretser et al. (1972) in all 5 patients studied found elevated FSH levels in the plasma and low plasma testosterone in half the cases. The plasma LH was elevated in half the cases and within the normal range in the remaining cases. Our data show a monotropic increase in urinary FSH in patients with the Sertoli-cell-only syndrome, the mean increase being 3.5 times the control which is statistically highly significant (Fig. 2, $P < 0.0005$). Although there is a considerable overlapping of the values in the 2 groups, and in fact half the cases fall within the normal

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Fig. 4.
FSH/LH ratio in 12 patients with the Sertoli-cell-only syndrome compared to FSH/LH ratio of normal and castrated men. Logarithmic scale.
Each point indicates 1 subject.
range, it should be realized that the 2 groups belong to 2 different populations, where the lowest value in the Sertoli-cell-only group should be compared with the lowest normal value. Seen from this point of view all FSH values are elevated. However, the FSH was far from the levels seen in castrated men (Fig. 2). None of the patients showed LH excretion higher than the highest normal value (Fig. 3), and the mean was not different from that of the controls, but in one patient (case 7) LH was slightly above the upper 95% fiducial limit (Table 2). The FSH/LH ratio was elevated to a level as seen in castrated men (Fig. 4).

In 2 patients we found the excretion of testicular androgen metabolites (androstene + aetiocholanolone) below the normal range (cases 7 and 8, Table 2). These 2 patients had pronounced hyperplasia of the Leydig cells, but so had patients with a normal excretion of these metabolites (cases 1, 2 and 10) and thus there is no direct correlation between the excretion of testicular androgen metabolites and the hyperplasia of the Leydig cells. All 6 males in whom a DXM-HCG test was performed (cases 1, 2, 7, 8, 9 and 10) had a normal response, i.e. a normal reserve capacity of the Leydig cells. As a feedback mechanism between LH and testosterone has been well established it is remarkable that LH is not elevated in the 2 patients with extremely low urinary testicular androgen metabolites. This fact indicates that the previous concepts that the LH-testosterone axis is always normal in males with impaired spermatogenesis is erroneous, at any rate when germ cells are completely absent. The lack of LH elevation and the normal response to HCG stimulation suggests that the disturbance primarily affects the hypophyses but the cause of the Leydig cell hyperplasia still remains obscure and raises the question whether the increased FSH production is involved in this mechanism.

Our findings of elevated FSH levels in the Sertoli-cell-only syndrome supports the concept that the germinal epithelium produces a substance capable of inhibiting the FSH secretion from the hypophyses and are thus in agreement with the reports of Paulsen (1968), Rosen & Weintraub (1971), Hilfrich et al. (1970), Franchimont et al. (1972), Mauss & Börsch (1973) and Kjessler & Wide (1973). The fact that FSH in the Sertoli-cell-only syndrome is significantly lower than the FSH in castrated males indicates that the Sertoli cell itself produces a basal amount of this inhibitor, the production site and chemically nature of which still remains obscure. In a subsequent paper on the relationship between spermatogenesis and the FSH and LH levels in oligospermic males this whole problem will be discussed in more detail.

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