URINARY FOLLICLE STIMULATING HORMONE
AND LUTEINIZING HORMONE IN
SIX MALES WITH THE XYY SYNDROME

By

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ABSTRACT

Urinary follicle stimulating hormone (FSH) and luteinizing hormone (LH) were studied in 6 males with karyotype 47, XYY and compared to FSH and LH in 14 normal males of the same age. FSH was within the normal range in all 6 subjects, LH however was markedly elevated in one case. The FSH/LH ratio was thus decreased in one case but normal in the remaining 5 cases. The mean excretion of FSH and LH did not differ significantly from that of normal males.

Previous studies of urinary or plasma levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in males with a 47, XYY chromosomal pattern have presented conflicting data. Up to the present 23 cases have been reported. In all cases a determination of LH was made but only in 10 cases were FSH analyses performed. Generally FSH was within the normal range whereas LH in half the cases was elevated while in the other half it was within the normal range (Papanicolaou et al. 1968; Hudson et al. 1969; Parker 1969; Santen et al. 1970; Shapiro 1970) (Table 1, cf. below).

The present study of 6 males with the XYY syndrome has been based on this background.
Table 1.

Urinary or serum levels of follicle stimulating hormone (FSH) and/or luteinizing hormone (LH) in males with the XYY syndrome.

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>FSH</th>
<th>LH</th>
<th>FSH/LH</th>
<th>Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>Increased</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Hudson et al. (1969)</td>
<td>5</td>
<td>Not assayed</td>
<td></td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Parker (1969)</td>
<td>7</td>
<td>Not assayed</td>
<td></td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Santen et al. (1970)</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Total (serum)</td>
<td>19</td>
<td>6</td>
<td>1</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Papanicolaou et al. (1968)</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Shapiro (1970)</td>
<td>1</td>
<td>Not assayed</td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>The present study</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Total (urine)</td>
<td>10</td>
<td>9</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total (serum + urine)</td>
<td>29</td>
<td>15</td>
<td>1</td>
<td>16</td>
<td>13</td>
</tr>
</tbody>
</table>
MATERIAL AND METHODS

Patients
The 19 patients were found in prevalence and incidence studies in the two Danish institutions for criminal psychopaths, in a forensic psychiatric clinic and a prison for young people as well as in a psychiatric hospital. The 8 patients were found outside institutions in population studies among males examined for military service and in medical wards; one of them (No. 75) was studied by Philip et al. (1970) in an investigation on infertile males.

The 6 males examined were those in whom it was possible to get reliable urine collection during at least 8 days.

None of the patients were chronically institutionalized, those who were in institutions had been there for no more than a few months, and none of them were given any medication. Their age varied from 19 to 29 years, the average age being 23.5 years. They each collected 8–12 24 hour urine samples, which were extracted by the method of Johnsen (1958), pooled and divided into 2 portions for the 2 bioassays. The 6 patients studied have previously been described with regard to their physical and mental states (Nielsen 1968 (No. 40 is case 3); Nielsen 1969 (No. 29); Skakkebæk et al. 1970 (No. 75); Nielsen 1971 (Nos. 67, 78 and 86)). Investigation of urinary total hypophysyal gonadotrophins and 17-ketosteroids in 12 of the 26 patients from the Cyto¬genetic Laboratory, Risskov, has been made by Nielsen & Johnsen (1973). The case numbers in the different publications correspond with the exception mentioned above.

All 6 patients had testes of normal size and consistency. Case No. 78 had clinical signs of hypogonadism (scanty pubic and axillary hair, no beard); the remaining 5 however were normally virile.

Controls
Fourteen normal, healthy males with an age span of 21–30 years, the average age being 23.9 years served as controls. They were normally virile without any sign of endocrine disorder, had testes of normal size and consistency and those who were married and wanted children had proved their fertility by having at least one child. The mean excretion of FSH was 5.4 IU/day (95% limits 2.0–14.8) and of LH 6.5 IU/day (95% limits 2.6–16.3). The average FSH/LH ratio was 0.83, the 95% limits being 0.3–2.3. All means are geometric means (antilog of mean log values, cf. below).

Bioassays
1. 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 Second International Reference Preparation for Human Menopausal Gonadotrophin (2. IRP-HMG) with a 3 + 3 design expressing the activity in IU per 24 h, 5 rats per dose.

2. The urinary LH was measured by the ventral prostate weight method (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, 5–8 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

As the excretion of hypophyseal gonadotrophins shows a log-normal distribution all values were transformed into logarithms in the statistical calculations and all means are accordingly geometric means. Table 2 shows the results of the bioassays. FSH was one the borderline of detection in cases 67 and 86 but all 6 patients had values within the normal range and the mean did not differ significantly from that of normal men ($t = 0.2, P < 0.45 > 0.40$). LH was highly elevated in case 75 but within the normal range in the remaining 5 cases and the mean was not statistically significantly higher than that of normal men ($t = 1.0, P < 0.20 > 0.15$). The FSH/LH ratio was below the normal range in case 75, the mean however did not differ significantly from that of normal men ($t = 1.1, P < 0.15 > 0.10$).

DISCUSSION

Table 1 shows the results of the previous studies as well as of the present ones. A total of 29 patients have been investigated. In all cases LH was determined, but the FSH was only determined in 16 of the subjects. Generally FSH was found to be within the normal range being only significantly elevated in 1 case and as this subject also had elevated LH the FSH/LH ratio was normal. LH

Table 2.

Urinary follicle stimulating hormone (FSH) and luteinizing hormone (LH) in 6 patients with the XYY syndrome. Comparison with normal subjects.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>FSH IU/day</th>
<th>LH IU/day</th>
<th>FSH/LH ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>29</td>
<td>12</td>
<td>6</td>
<td>2.00</td>
</tr>
<tr>
<td>40</td>
<td>23</td>
<td>6</td>
<td>3</td>
<td>2.00</td>
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<tr>
<td>67</td>
<td>24</td>
<td>2</td>
<td>3</td>
<td>0.67</td>
</tr>
<tr>
<td>78</td>
<td>20</td>
<td>6</td>
<td>11</td>
<td>0.56</td>
</tr>
<tr>
<td>86</td>
<td>19</td>
<td>2</td>
<td>4</td>
<td>0.50</td>
</tr>
<tr>
<td>75</td>
<td>26</td>
<td>10</td>
<td>74</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Mean

<table>
<thead>
<tr>
<th></th>
<th>Geometric mean</th>
<th>95 % limits</th>
<th>Geometric mean</th>
<th>95 % limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.1</td>
<td>1.1-23.7</td>
<td>6.5</td>
<td>2.0-14.3</td>
</tr>
<tr>
<td>Controls</td>
<td>23.9</td>
<td>0.8-101.9</td>
<td>0.83</td>
<td>0.3-2.3</td>
</tr>
</tbody>
</table>

628
was elevated in 13 cases but was in the normal range in the remaining 16 cases. The FSH/LH ratio was decreased in 4 of 16 cases but within the normal range in the other 12 cases.

The serum determinations were generally in agreement with the urine determinations. However, all cases with decreased FSH/LH ratio were studied, using bioassays on extracts of urine and 3 of the 4 cases were described by Papanicolaou et al. (1968). It is possible that the different results obtained by these investigators and by us could be explained on methodological grounds. Papanicolaou et al. (1968) used the ovarian ascorbic acid depletion method (OAAD) for the determination of LH; we however used the ventral prostate method in hypophysectomized rats (VPW). In our laboratory it has been shown that the former method is highly unspecific whereas the latter is specific for LH (Koed & Hamburger 1968; Christiansen 1968). Papanicolaou et al. (1968), performing 4–5 LH analysis in each subject over a period of 10 days, found in 2 of the 3 cases pronounced day-to-day variation in the excretion of LH, the LH of some of the days being within the normal range. The excretion of FSH and LH was compared to that of 9 normal men reported by Becker & Albert (1965). These normal males were however appreciably older than the 3 subjects investigated and were selected among normals having the highest excretion of total hypophyseal gonadotrophins.

However, it seems unlikely that differences based on methodological grounds could be the only explanation of the different results obtained and in fact we found a highly elevated LH in one of our patients. The XYY syndrome is not necessarily a uniform type of syndrome, since there may be biological differences from one patient to another. Thus for instance there may be one group with normal levels of LH and another group with elevated LH. Differences in the ascertainment of the XYY patients from one study to another may also to a certain extent account for the differences in FSH and LH levels. Up to the present few patients have been studied to allow of any certain conclusion of this problem, especially since testicular biopsies and studies on the androgen metabolism in such patients have not been performed in combination with the gonadotrophin studies.

Skakkebæk et al. (1971) made a survey of all studies on testicular biopsies from XYY males published before 1970, comprising a total 20 patients. No specific histological changes were observed but only in 4 cases spermatogenesis was normal. Skakkebæk et al. (in press) further studied 4 XYY males from a general population study, 3 of them had severe impairment of spermatogenesis and it was concluded that the germinal epithelium is impaired in the majority of such patients. One of our patients (No. 75, the one with the elevated LH) had a biopsy of the testes, showing the usual picture of the XYY syndrome: varying degree of sclerosis and hyalinization of some tubular membranes, partial or total spermatogenic arrest and some Sertoli-cell-only tubules. No
Leydig-cell hyperplasia was observed. On this background it is surprising that FSH in this patient is within the normal range as usually FSH increases when spermatogenesis is impaired, whatever the reason. The finding that LH is increased is also surprising as no Leydig-cell hyperplasia was seen and the excretion of testicular androgen metabolites in most such patients is at a normal level (Nielsen & Johnsen 1973).

Further studies are necessary to reveal the mechanism of the hypophyseal-testicular axis in patients with the XYY syndrome and particularly in studies on testicular biopsies, androgen metabolism and FSH and LH in both urine and plasma.

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REFERENCES


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