URINARY EXCRETION OF ADRENAL HORMONES IN GONADAL DYSGENESIS AND ITS RESPONSE TO CORTICOTROPHIN AND GONADOTROPHIN STIMULATION

By

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ABSTRACT

The functional capacity of the adrenals was studied in eight adult patients with gonadal dysgenesis, ranging in age from 16–42 years, by measuring the 24-hour urinary excretion of 17-hydroxycorticosteroids (17-OHCS) and of 17-ketosteroids (17-KS) with the patient at rest and also by estimating its response to stimulation with corticotrophin and chorionic gonadotrophin.

In six patients the clinical diagnosis of the syndrome was confirmed by laparotomy, when no gonads were found in five patients and a white fibrous band replacing the gonads was found in the other. The remaining two patients of the series both had male sex-chromatin.

The resting excretion of both 17-OHCS and 17-KS was within normal limits in all eight patients.

After corticotrophin stimulation (25 IU infused over 8 hours) an increased 17-OHCS excretion was found in all patients but the increase was less constant for the 17-KS. These results are identical with those expected from normal subjects and were considered to indicate a normal adrenal secretory capacity in the present cases.

Stimulation by chorionic gonadotrophin (HCG test) was performed in four patients using various doses of the hormone, namely 1500 IU for 5 days, 5000 IU for 2 or 5 days, or 10 000 IU for 2 days. Three of these patients had no gonads and the fourth had male sex-chromatin. The HCG test failed to elicit an increased excretion of either 17-OHCS or 17-KS in these patients. This absence of response is regarded as evidence that HCG does not stimulate adrenal tissue to secrete the precursors of these hormones.

The findings of the present study are discussed in the light of previous publications.
Early investigators of gonadal dysgenesis considered the functional state of the adrenal glands to be deficient in this syndrome (Albright et al. 1942). This view was based mainly on the low 17-ketosteroid excretion which was found and which has since been confirmed in some other series (Albeaux-Fernet & Deribreux 1955; Grumbach et al. 1955; Netter et al. 1957).

Some publications, however, especially those concerning adult cases of the syndrome, report a normal 17-ketosteroid (17-KS) excretion in almost all patients (Del Castillo & Argonz 1951; Hortling & Jäämeri 1953; Hoffenberg & Jackson 1957; Sele & Trolle 1960; Hauser 1961). Urinary corticosteroids were also found to be normal in the few cases in which they were estimated (Netter et al. 1957; Bahner & Schwarz 1959; Hauser 1961). Frank clinical adrenal insufficiency has not been encountered in association with the syndrome. Corticotrophin (ACTH) stimulation, on the other hand, has given conflicting results (Winckelmann 1954; Hoffenberg & Jackson 1957; Netter et al. 1957; Michard 1958; Bahner & Schwarz 1959; Bailey et al. 1960).

This lack of agreement has prompted us to report, in this paper, a study of the functional capacity of the adrenals in eight adult patients with gonadal dysgenesis, using ACTH and gonadotrophin stimulation.

MATERIAL AND METHODS

Eight adult patients with the gonadal dysgenesis syndrome were studied. Their ages ranged from 16-42 years.

Table 1.
Clinical and laboratory findings in eight patients with gonadal dysgenesis.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>FSH (mouse units)</th>
<th>Sex chromatin</th>
<th>Laparotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) RO.</td>
<td>16</td>
<td>1.43</td>
<td>42</td>
<td>+200</td>
<td>3</td>
<td>Infantile uterus</td>
</tr>
<tr>
<td>2) BE.</td>
<td>44</td>
<td>1.35</td>
<td>34</td>
<td>+100</td>
<td>3</td>
<td>Absence of ovaries</td>
</tr>
<tr>
<td>3) MAR.</td>
<td>19</td>
<td>1.42</td>
<td>32</td>
<td>+50</td>
<td>3</td>
<td>Absence of ovaries</td>
</tr>
<tr>
<td>4) COL.</td>
<td>21</td>
<td>1.37</td>
<td>42</td>
<td>+200</td>
<td>3</td>
<td>Hypoplastic uterus</td>
</tr>
<tr>
<td>5) AG.</td>
<td>48</td>
<td>1.49</td>
<td>55</td>
<td>+ +25</td>
<td>3</td>
<td>Absence of ovaries</td>
</tr>
<tr>
<td>6) AG.</td>
<td>20</td>
<td>1.38</td>
<td>38.5</td>
<td>+200</td>
<td>3</td>
<td>Absence of ovaries</td>
</tr>
<tr>
<td>7) LES.*</td>
<td>23</td>
<td>1.68</td>
<td>55</td>
<td>+100</td>
<td>F</td>
<td>Infantile uterus and Fallopian tubes</td>
</tr>
<tr>
<td>8) LIG.</td>
<td>19</td>
<td>1.55</td>
<td>42</td>
<td>+ +25</td>
<td>3</td>
<td>Absence of ovaries</td>
</tr>
</tbody>
</table>

*) This patient has been previously reported (Laroche et al. 1958).
The diagnosis, based on clinical and laboratory investigation, was confirmed in six of the cases by exploratory laparotomy (Table 1). In five of these patients no gonads were found at operation, whereas in the sixth, two white fibrous bands were seen in place of the ovaries. Histological examination of these bands revealed no germinal cells. In the remaining two patients, no laparotomy was performed and the presence of male sex-chromatin was considered adequate confirmation of an otherwise clinically evident diagnosis.

The intravenous ACTH test was performed in the usual way: 25 IU of ACTH in 500 ml of saline solution were infused over an 8-hour period, starting at 8 a.m. The urine was collected for hormone estimations on one or more days prior to the test, on the day of the test itself and again on the following day.

In four patients an attempt was made to stimulate the adrenals with chorionic gonadotrophin (HCG test). As this test has not been standardized, various doses and methods of administration were used, although the hormone was always given intra-muscularly. The following dosage schedules were employed: 1500 IU for 5 consecutive
days, 5000 IU for 2 or 3 days and 10 000 for 2 days. The urine was collected for analysis on the day of the last injection.

In one patient (G.A., Fig. 1) the HCG test preceded the ACTH test by one month. In the remaining three it was performed 7–20 days after the ACTH test. In two of these three patients a second ACTH test was performed 5–15 days after the HCG test.

The 17-hydroxycorticosteroids (17-OHCS) were estimated by the method of Porter & Silber (1950). The normal values for women obtained in our laboratory by this method are 2.5–6 mg/24 h. The 17-KS were measured by the method of Cahen & Salter (1944). The normal values for women obtained in our laboratory by this method range from 5.5–14 mg/24 h. Day-to-day variations in normal subjects are usually found to lie within these limits.

After ACTH stimulation, it is normal to obtain an excretion of 17-OHCS from 6–20 mg/24 h. Values outside this range are rarely if ever obtained in normal subjects and are considered to indicate hyper- or hypo-function of the adrenals. The response of 17-KS to ACTH stimulation, however, is less constant and less pronounced, often not exceeding the limits of the expected daily variation. Nevertheless, an increase after ACTH of a previously low 17-KS output, even if it does not exceed the upper normal limit, has some significance from a clinical point of view in excluding adrenal insufficiency. Occasionally a marked 17-KS response also adds significance to a 17-OHCS response which is only moderate.

**RESULTS**

The excretion of 17-OHCS during the control days prior to the test was normal, apart from some of the assays in two patients. In one of these (COL., Fig. 1) a low excretion of 17-OHCS (1.2 mg) was found on the first control day. This was accompanied, however, by a normal output of 17-KS (11.6 mg) and was followed on the next day by a wholly normal value for 17-OHCS (3.2 mg). In the other patient (GA., Fig. 1) the excretion of 17-OHCS on the second and third control day was low, without any concomitant depression of 17-KS excretion; moreover the output of both 17-OHCS and 17-KS was normal on the first and fourth control days.

The 17-ketosteroid output was normal for all patients with the exception of a single assay (LIG., Fig. 1) in which the low value of 4.1 mg was found. The remainder of the assays ranged from 5.6 mg to 11.6 mg with a mean of 8.2 mg/24 h.

After ACTH stimulation there was a rise in the excretion of 17-OHCS in all patients, their output on the day of ACTH administration varying from 8.0 mg to 15.3 mg with a mean of 10.7 mg/24 h (Fig. 1). This response, in relation to the mean output of 3.4 mg/24 h obtained before the ACTH, is considered to indicate a normal adrenal secretory capacity in these patients.

The 17-KS excretion on the day of ACTH infusion exceeded the normal upper limit in three of the patients (GA., LES., and LIG., Fig. 1) and rose to approximately double the control values obtained before ACTH. In the remaining five cases, little or no increase in 17-KS excretion was observed.
After the chorionic gonadotrophin injection, no change in output of either 17-OHCS or 17-KS was observed with any of the doses used.

**DISCUSSION**

These results indicate a normal adrenal secretory capacity in all the cases of the present series. In particular, the resting excretion of both 17-OHCS and 17-KS was within the normal range in all patients. However, other workers have sometimes found a low 17-KS output in patients with gonadal dysgenesis. The excretion of these metabolites is normally low before puberty, and a low value obtained in the patients at this age is therefore difficult to evaluate; a decreased excretion in adults is more significant. For this reason and because all the patients of the present series were over 16 years of age, only the literature concerning series of adults with the syndrome need be reviewed here.

A low excretion of 17-KS, *i.e.* under 5 mg/24 h, has been found in 20 out of the 27 adult patients with gonadal dysgenesis reported in the work of Albright et al. (1942), Grumbach et al. (1955), Albeaux-Fernet & Deribreux (1955) and Netter et al. (1957). Other workers in the other hand, encountered a considerably smaller proportion of cases with a low output; only 5 such cases appear in a total of 55 reported by Del Castillo & Argonz (1951), Hortling & Jäämeri (1953), Hoffenberg & Jackson (1957), Sele & Trolle (1960) and Hauser (1961). In a series of 28 cases, of which 11 had a low output, reported by Briggs & Kupperman (1956) and Teter & Tarlowski (1958), the proportion was intermediate.

A possible cause of this seeming discrepancy may have been the inclusion, in the first group of publications mentioned above, of a higher proportion of cases of gonadal dysgenesis with the typical short stature and associated cardiovascular and renal anomalies, since both body-surface and the presence of congenital malformations are known to affect the excretion of 17-KS. In support of this view is the fact that many patients in the series of Sele & Trolle (1960) and of Hauser (1961), in which most patients were found to have a normal output, were of normal height. In the present series, however, there was no correlation between body-surface and hormonal output. Indeed, the five patients with a relatively small body-surface (height under 1.43 metres, weight under 42 kg) gave a mean 17-KS output of 9 mg as compared with a mean of 7.9 mg excreted by the remaining three patients of larger stature.

The corticosteroid output has only been estimated in a small number of patients with gonadal dysgenesis and has generally been found to be normal (Netter et al. 1957; Bahner & Schwarz 1959; Hauser 1961). Our own results are in agreement with this finding.

Adrenal stimulation by ACTH has had variable effects in gonadal dys-
genesis. Bailey et al. (1960) reported one case with a normal excretory response; Michard (1958) states that he obtained a normal response to ACTH in two cases. Netter et al. (1957) also observed a normal response in one case. Hoffenberg & Jackson (1957) report a positive Thorn test in six patients. On the other hand, failure of the adrenals to respond to ACTH has been reported in one case of gonadal dysgenesis by Winckelmann (1954) and in another by Bahner & Schwarz (1959). Moreover, with the exception of Bailey et al. (1960), those authors who observed positive excretory responses did not mention the output values obtained.

In all patients of the present study, ACTH stimulation produced a normal response, i.e. a constant increase in 17-OHCS excretion and a less marked rise in 17-KS output (Fig. 1). However, in all our cases the resting excretion was normal and it would be interesting to know the response to ACTH stimulation of patients with a low resting output.

In so far as an adrenocortical response can be inferred from an increased urinary excretion of 17-OHCS and 17-KS in patients with this syndrome, chorionic gonadotrophin did not appear to stimulate the adrenal cortex in the four patients of the present series on whom the HCG test was performed. Failure of the 17-KS to respond to the HCG test was also noted by Gordan et al. (1955) in two cases of gonadal dysgenesis with androgenic manifestations. However, these workers did not estimate the capacity of the adrenals in their cases to respond to ACTH. Bahner & Schwarz (1959) have also reported a case with androgenic features in which neither ACTH nor HCG produced a positive urinary response. Elliot et al. (1959) failed to find an increase in 17-KS output after HCG, in two cases of gonadal dysgenesis, although they report the interesting finding on an increased oestrogen output. The negative results of the HCG test in four patients of the present series, in whom the normal response of the adrenals to ACTH had been demonstrated, support the conclusion that chorionic gonadotrophin does not stimulate the adrenal cortex to produce the precursors of 17-OHCS or of 17-KS.

REFERENCES


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