HYPOPHYSO-GONADAL FUNCTION IN THE CRYPTORCHID CHILD: DIFFERENCES BETWEEN UNILATERAL AND BILATERAL CRYPTORCHIDS

By

E. Cacciari, A. Cicognani, P. Pirazzoli, F. Zappulla, P. Tassoni, F. Bernardi and S. Salardi

ABSTRACT

In 22 normal boys, 33 unilateral and 14 bilateral cryptorchids, a gonadal function test (2000 IU of HCG im each a day for three days and assays of plasma testosterone and plasma oestradiol-17β before and after the HCG administration) as well as an LH-RH test were carried out. In 60% of the cases, both normal and cryptorchid boys, plasma oestradiol-17β (both in basal conditions and after stimulus) were found to be less than the sensitivity (5 pg/ml) of the method. While the plasma testosterone was similar under basal conditions in the three groups of children, after HCG it was significantly lower than the mean value of the control group only in the bilateral cryptorchids. The testosterone levels, both under basal conditions and after stimulus, are correlated to bone age only in the normal boys and in the unilateral cryptorchids. There were no significant differences among the various groups for either LH and FSH both under basal conditions and after LH-RH. The LH curve area during the LH-RH test is in correlation with bone age only in the normal children.

The scanty data regarding the endocrine function (Rivarola et al. 1970; Zachmann 1972; Sizonenko et al. 1973; Canlorbe 1974; Cacciari et al. 1974a) as well as the histological pattern of the gonads (Mancini et al. 1965; Bramble et al. 1974; Canlorbe 1974), and the pituitary reserve of gonadotrophins (Job et al. 1974) also provide further support to this fact.
in the pre-pubertal cryptorchid boy do not yield a clear picture of the hypothalamo-pituitary-gonadal situation of these patients, even though they provide useful data for discussion. As a matter of fact, the results of the various investigations usually do not refer to the same children and moreover, in the studies of the various investigators, all the children belonging to the pre-pubertal stage are put in one group, regardless of their age, whereas it is known that during the pre-pubertal stage the behaviour of testosterone after HCG and of LH after LH-RH varies according to the bone age (August et al. 1972; Cacciari et al. 1974a,b).

Bearing this in mind, we have studied the pituitary-gonadal axis in a group of pre-pubertal uni- and bilateral cryptorchid boys.

**MATERIALS AND METHODS**

Twenty-two normal boys (chronological age ranged from 5 to 11 7/12 years, mean 8 7/12; bone age ranged from 4 8/12 to 11 7/12 years, mean 8 6/12), 33 unilateral cryptorchids (chronological age ranged from 4 to 11 2/12 years, mean 8 7/12; bone age ranged from 4 to 11 years, mean 8 5/12) and 14 bilateral cryptorchids (chronological age ranged from 4 to 11 3/12 years, mean 8 7/12; bone age ranged from 4 to 11 years, mean 8 6/12) were studied. In all the cases examined, the difference between the chronological and the bone age was never greater than six months.

All the children examined fell into the pre-pubertal stage of sexual development, i.e. the 1st stage according to Tanner (1962). None of the cryptorchid boys had undergone medical treatment or surgery in order to modify the abnormal position of the testes. The undescended testes were always located in the inguinal canal. Bilateral cryptorchids without palpable gonads were excluded to avoid taking the anorchid subjects into consideration. Moreover, all the boys with retractile testes were also excluded. None of the patients was found to have a pituitary defect.

All the children, with permission from the parents, underwent both a gonadal function and a LH-RH test. The gonadal function test was carried out in the following manner: HCG was administered in a dose of 2 000 IU im every day for three days. The dose was administered at 9:00 a.m. on the first two days, and at 6:00 a.m. on the third day. Immediately before the beginning and at the end of the test a blood sample was collected to assay plasma testosterone and plasma oestradiol-17β. The LH-RH test was performed at 9:00 a.m. after an overnight fast, using intravenous injection of 50 μg of synthetic LH-RH (Farbwerke Hoechst AG). Venous blood for the evaluation of LH and FSH was collected at times 0, 15, 30, 60 and 90 min.

Bone age was determined according to the tables of Greulich & Pyle (1959). Plasma oestradiol-17β was assayed according to the radioimmunoassay method of Emment et al. (1972) using an antiserum at a dilution of 1:30,000 as previously described (Cacciari et al. 1974a). The sensitivity of the method was 5 pg/ml. The variation coefficient of duplicate samples was ± 10%.

Plasma testosterone was determined according to the radioimmunoassay method of Collins et al. (1972). The antiserum we used was obtained from rabbits pre-treated with an anti-tubercular vaccine as previously described (Cacciari et al. 1974a). The antiserum was used at a dilution of 1:30,000. The sensitivity of the method was 0.5 ng/100 ml. The variation coefficient of duplicate samples was ± 4.2%.

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Table 1.
Plasma testosterone behaviour in basal conditions and after HCG in 22 normal children, in 33 unilateral and 14 bilateral cryptorchids.

<table>
<thead>
<tr>
<th>No.</th>
<th>Basal testosterone (ng/100 ml)</th>
<th>After HCG testosterone (ng/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
</tr>
<tr>
<td>Normal children</td>
<td>22</td>
<td>15.40</td>
</tr>
<tr>
<td>Cryptorchids</td>
<td>47</td>
<td>18.65</td>
</tr>
<tr>
<td>Unilateral cryptorchids</td>
<td>33</td>
<td>20.03</td>
</tr>
<tr>
<td>Bilateral cryptorchids</td>
<td>14</td>
<td>15.40</td>
</tr>
</tbody>
</table>

* Significantly different from the after HCG testosterone of normal children \( P < 0.05 \).

Serum LH and FSH were evaluated according to the double antibody radioimmunoassay method of Reuter et al. (1973), using human pituitary LH and FSH (the radioimmunological equivalent of LH is 2150 IU as compared to the 68/40 reference preparation of the National Institute for Medical Research (MRC), Mill Hill, London. For FSH this is 2800 IU as compared to the 68/39 reference preparation of MRC. The results are expressed as mIU/ml MRC reference preparation. The sensitivity of the method was 0.5 mIU/ml, both for LH and FSH. The variation coefficient of duplicate samples was ± 7.4 % and ± 8.5 % for LH and FSH respectively.

For the statistical analysis of the results, Student's \( t \)-test was used and the correlation coefficient \( r \) was calculated.

RESULTS

In more than 60 % of the cases, both among normal boys and cryptorchids, the plasma oestradiol-17β, both in basal conditions and following stimulus, was always less than 5 pg/ml. In 18 % of the cases among the unilateral cryptorchids and in 22 % of the normal subjects and of the bilateral cryptorchids, oestradiol-17β increased significantly after the stimulus and this increase was not in correlation with the bone age.

The mean basal testosterone level does not show any significant differences among the three groups examined (Table 1). After stimulus with HCG in the unilateral cryptorchids, the mean testosterone level is not significantly different from the mean value of the control group, whereas in the bilateral cryptorchids it was significantly lower \( P < 0.05 \). There is a highly significant positive
correlation in the normal children \((r = +0.718, P < 0.01, \text{Fig. 1})\) between bone age and basal testosterone. The unilateral cryptorchids behaved like the control group, while the above-mentioned correlation was not present in the bilateral cryptorchids (Fig. 1). After stimulus with HCG the behaviour of the above-mentioned correlation was completely similar. The only difference was to be found in degree of significance \((P < 0.05, \text{Fig. 2})\).
Fig. 3.
FSH and LH behaviour (mean ± SEM) in normal and cryptorchid children who underwent the LH-RH test (50 µg iv).

Table 2.
Maximum peak, maximum increase and area of the LH and FSH curves (mean ± SEM) in the LH-RH test.

<table>
<thead>
<tr>
<th>No.</th>
<th>Maximum peak</th>
<th>Maximum increase</th>
<th>Area of the curve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LH (mIU/ml)</td>
<td>FSH (mIU/ml)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LH (mIU/ml)</td>
<td>FSH (mIU/ml)</td>
<td></td>
</tr>
<tr>
<td>Normal children</td>
<td>22</td>
<td>4.52 ± 0.66</td>
<td>2.56 ± 0.65</td>
</tr>
<tr>
<td>Cryptorchids</td>
<td>47</td>
<td>4.01 ± 0.40</td>
<td>2.00 ± 0.30</td>
</tr>
<tr>
<td>Unilateral cryptorchids</td>
<td>33</td>
<td>4.02 ± 0.43</td>
<td>2.12 ± 0.41</td>
</tr>
<tr>
<td>Bilateral cryptorchids</td>
<td>14</td>
<td>3.97 ± 0.88</td>
<td>1.75 ± 0.28</td>
</tr>
</tbody>
</table>
The mean LH and FSH behaviour during the LH-RH test did not reveal significant differences between the normal and cryptorchid boys (Fig. 3). However, the mean LH curve in both the unilateral and bilateral cryptorchids was constantly lower than that of the control group, whereas the mean FSH curve in the unilateral cryptorchids was exactly the same as that found for the normal boys, and in the bilateral cryptorchids it was higher than that of the control group (Fig. 3). The pituitary gonadotrophin reserve that was studied by evaluating the maximum peak, together with the maximum increase and the area of the curve (Table 2), did not present any significant differences in the various groups of children. Both in the normal and the cryptorchid children there was no correlation between bone age and basal value or pituitary reserve of FSH.

As far as LH is concerned, we noted a positive correlation between the maximum peak \((r = + 0.431, P < 0.05)\) or area of the curve \((r = + 0.621, P < 0.01)\) and bone age only in the normal boys. No correlation was found between LH and testosterone both under basal conditions and after stimulus. As far as FSH is concerned, we found a positive correlation between this hormone and testosterone in the unilateral cryptorchids in basal conditions \((r = + 0.660, P < 0.01)\).

No sample examined turned out to be undetectable either for LH or FSH, and in the cryptorchids the responses to the LH-RH for both the gonadotrophins were never found to be outside the range of the control group.

**DISCUSSION**

The low sensitivity of our method did not enable us to reach definite conclusions concerning the plasma oestradiol-17\(\beta\) behaviour, although it is realised how unprepared the male gonad (whether undescended or normally descended) may be to produce oestradiol-17\(\beta\) during the pre-pubertal stage of development (Winter et al. 1972; Cacciari et al. 1974a; Canlorbe 1974).

The behaviour of testosterone after stimulus leads us to make some observations. Even though we do not find significant differences between the unilateral and bilateral cryptorchids, we cannot consider these two groups as being the same. As a matter of fact, when comparing the mean testosterone response from the two groups taken separately with the normal group of children, we find that in both cryptorchid groups the response is lower than that in the control group, while there is a significant difference only between normal subjects and the bilateral cryptorchid boys. One difference between unilateral and bilateral cryptorchids is clearly confirmed by the lack of correlation in the bilateral cryptorchids between bone age and testosterone, both under basal conditions and after stimulus. The importance of this finding is evident. In fact, if the equality between unilateral and bilateral cryptorchids is evidence for the primitive nature of the testicular damage in cryptorchidism, a difference between
the two situations leads us to consider seriously, also the wrong position at least as far as the endocrine function is concerned.

In the cryptorchids Job et al. (1974) found a maximum LH peak after LH-RH that was significantly lower than that of the control group. We did not find any difference between the normal boys and the uni- and bilateral cryptorchids, either in basal conditions or after stimulus, both for LH and FSH. We should point out, however, that among the cases of Job et al. (1974) there are also two patients included in the mean who did not respond to the releasing and who therefore could have been carriers of a complex hypogonadism so that their cryptorchidism could only have been a symptomatic factor.

The positive correlation observed in the normal boys but not in the cryptorchids between bone age and maximum LH peak and area of the LH curve leads us to advance the hypothesis that in cryptorchidism even the regular development of the hypothalamo-pituitary axis is altered, and that the secretion of gonadotrophins is, possibly, involved in the retarded testicular maturation which is a feature of this disease (Canlorbe 1974; Canlorbe et al. 1974).

Swerdloff et al. (1972) demonstrated that in hypophysectomized rats FSH plays an important role in controlling the secretion of testosterone. Sizonenko et al. (1973) pointed out that in the cryptorchid boy FSH is a mediator of the gonadal secretion of testosterone. We found a highly significant correlation between basal testosterone and FSH only in the unilateral cryptorchids. While on the one hand, this finding confirms the results of Sizonenko et al. (1973), on the other, it leads us to advance the hypothesis that the above mentioned FSH role is clearly seen only in some pathological conditions.

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REFERENCES


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