DAMAGE TO TESTICULAR FUNCTION IN CHRONIC RENAL FAILURE OF CHILDREN

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Summary

The functional endocrine reserve of testes was studied in 58 boys before and during puberty at different stages of chronic renal failure. Plasma testosterone (T) and dihydro-T were measured before and seven days after stimulation with human chorionic gonadotrophin (HCG). The T response to HCG often appeared to be already subnormal in renal failure before puberty had started. A negative correlation was observed in prepubertal boys between serum creatinine and stimulated T levels before the start of dialysis. During puberty the response to HCG was lower in boys on conservative treatment and on haemodialysis than after transplantation.

Introduction

In male adult patients with chronic renal failure (CRF) plasma testosterone (T) has repeatedly been reported to be decreased, usually in the presence of elevated levels of luteinising hormone (LH) [1]. After stimulation of the testes by human chorionic gonadotrophin (HCG) the rise of T is often diminished, compared to healthy adult males. This alteration occurs in the early stages of CRF and gets more pronounced with progressive deterioration of renal function and during haemodialysis treatment [2]. After transplantation endocrine function of the testis recovers, at least partially [3, 4].

Failure to grow and delay of puberty [5, 6] are well-known signs of CRF in paediatric patients. They might be related to insufficient androgen production in the uraemic stage. In the following study we have investigated in children at different stages of CRF whether the functional endocrine reserve of testicular tissue is already damaged before and during puberty.
Patients and methods

The study was performed in 58 male paediatric patients with CRF followed at the University Children’s Hospital, Heidelberg (n = 33) and at the Hôpital des Enfants malades, Paris (n = 25). The age varied between 2 and 15 (mean 10.6) years in the prepubertal group (n = 30) and 11 and 20 (mean 15.6) years during puberty (n = 28). In two patients the HCG test was performed twice on different forms of treatment.

At the time of the study 18 patients were on conservative treatment (CT), 22 on regular haemodialysis two to three times per week and 20 transplanted (TP). The CT patients had a serum creatinine level (SCR) ranging between 1.5 and 9.5 mg/dl. In HD patients treatment had been started 1 to 103 (mean 23) months before the study. TP patients were investigated in the absence of any signs of rejection after a period of at least three (usually ≥ 6) months on a low dose constant steroid treatment. The time after grafting ranged between 4.5 and 60 months with an average of 23 in prepubertal children and 26 months during puberty; in only six boys was it less than 12 months.

A commercial preparation of HCG, 5000 U/m² BSA, was injected three times per week (every second day) i.m. Heparinised blood was obtained before and seven days after the first injection of HCG. In dialysed patients the injections were given and blood was taken usually on the days between dialysis sessions. T and dihydrotestosterone (DHT) in plasma were measured by a radioimmunoassay sensitive enough to detect prepubertal hormone levels.

The clinical data obtained at the time of the study included body height and weight, skeletal age (hand x-rays), testicular size, development of genitalia, of pubic hair (Tanner’s stages) [8] and of axillary hair, SCR. In TP patients the dose of the prednisone immunosuppressive therapy was noted. The patients were subdivided according to the stage of pubertal development. They were regarded as prepubertal in the presence of Tanner’s stage 1 for development of genitalia and pubic hair and if testicular size was no more than 3ml. Bone age in prepubertal children varied between 0.5 and 12 (mean 7.5) years.

Results

The results were related to the mode of treatment and to the degree of pubertal development. In prepubertal boys with all modes of treatment basal T levels were slightly lower than in normal children [7] (Figure 1). After stimulation with HCG T levels rose in all patients but the median values attained were below the mean ± SE reported in normal prepubertal boys by Scholler et al: 288ng/dl on CT, 229 ng/dl on HD, 260ng/dl after TP vs 337 ± 43ng/dl in controls [7]. If the mean normal value is taken as 100%, the mean stimulated T (± SD) was 93 ± 41% on CT, 78 ± 26% on HD and 89 ± 32% after TP. The differences between the three treatment groups were not significantly different. However, in four out of 11 children on CT and in 3 of 11 on HD against none after TP, the increase of T was to less than 200ng/dl, i.e. below — 2SD the mean normal values [7]. The median stimu-
Figure 1. Plasma testosterone levels in 30 prepubertal boys before and after injection of three times 5000 units per m² of human chorionic gonadotrophin, i.m. Mean normal level according to Scholler et al [7]

lated DHT levels were 14.0ng/dl on CT, 17.9ng/dl on HD and 18.5ng/dl after TP (no significant differences).

During puberty basal and HCG stimulated T and DHT levels varied more than in prepubertal boys (Figure 2). Since T response to HCG varies greatly with the stage of puberty, the patients were subdivided according to the development of pubic hair (P2–P5). Whereas only 2/7 patients on CT and none of 11 on HD showed a stimulated T value above the average of the normal population at the corresponding pubertal stage [7], this was the case in 6 out of 11 TP boys (Figure 2). Compared to normal T response according to the P stage (= 100%) [7], the mean T (± SD) in the pubertal patients was 72 ± 44% on CT, 64 ± 27% on HD and 111 ± 38% after TP. By variance analysis the differences between all three groups were significant (F = 6.148, p < 0.01).

T levels were also analysed according to glomerular function. In the prepubertal group stimulated T appeared to fall with increasing concentrations of SCR (r = 0.70, p < 0.05). When related to 1/SCR T levels correlated even better (r = 0.79, p < 0.01).
Figure 2. Plasma testosterone levels in 28 pubertal boys before and after injection of three times 5000 units per m^2 of human chorionic gonadotrophin i.m. Pubertal stages according to Tanner [8]: P2 = ○, P3 = ▲, P4 and P5 = ■. Mean normal levels according to Scholler et al [7].

Discussion

A number of hypotheses have been proposed to explain the low T concentrations in adult males with CRF, among which damage to Leydig cell function by uraemic toxins seems to be the most important [1]. Either a basic defect in T production by Leydig cells or resistance of these to the action of LH could explain low T release in the presence of high blood levels of LH. Only a few data are available on androgen production in children with CRF. In some patients basal T was found to be low [5] whereas in another study normal values were reported [9]. Before puberty, the simple measurement of T gives little information on the functional capacity of the testes. The immature testis, however, is able to respond to stimulation with HCG, although less than in older subjects [7].

Our study suggests that in CRF damage to testicular tissue may already occur before and during puberty. Although before puberty T levels after stimulation with HCG were not significantly different in CRF from a normal group of children the inverse correlation between T and renal function suggests that the functional endocrine reserve of testes is reduced by uraemia before endogenous androgen production starts to increase along with the appearance of clinical signs of puberty.

During puberty we found a diminished response to T in many CT and HD patients whereas in transplanted boys the endocrine reserve of the testes never
appeared to be clearly abnormal (Figure 2). The better T response in TP patients compared to those on CT and on HD which was earlier observed in adults with CRF [2], might reflect a partial recovery of testicular function after a successful graft. The failure to find a similar difference in prepubertal children apparently was not related to a difference in time after grafting.

A critical point in our study is the application of control data from a series of children stimulated with HCG by a schedule slightly different from that in the CRF patients (1500 U x 3 vs 5000 U/m² x 3, both on alternate days). However, it appears that at least in prepubertal boys, post-stimulatory T levels are related rather to the duration of the test than to the dose of HCG injected [7]. Furthermore, the injection of 1500 U (absolute dose) in our patients would have corresponded to a lower dose per m² for most of our patients, resulting in a smaller rather than higher T response compared to that observed by us.

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References