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The Value of Testicular Biopsy in Cryptorchidism

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Summary. This prospective study conducted on 24 children, who have now reached adulthood, was undertaken to determine the value of testicular biopsies in cryptorchidism relative to fertility prognosis. A significant correlation between the number of germ cells in the biopsy and sperm count was found to exist ($p < 5\%$). Thus, the testicular biopsy performed during orchiopexy was found to have a prognostic value. The hormonal findings (LH, FSH) suggest that in cryptorchid adults impaired Leyding cell function exists only when serious tubular damage is present. Because of its prognostic value with respect to fertility and the probability of discovering carcinoma in situ cells, it is strongly recommended that a testicular biopsy is performed in cryptorchid boys.

Key words: Testicular biopsy, Cryptorchidism, Fertility, FSH, LH, T, Estradiol.

Introduction

Cryptorchidism is one of the most common malformations of an endocrine gland in the male population. Approximately one percent of the male population has one or both testes undescended [15]. Sterility and malignancy are the two main problems resulting from the cryptorchid state of the gonad. To interpret the hormonal status and testicular function in adult patients being treated prepubertally for cryptorchidism is difficult because it is impossible to distinguish between the hormonal consequences resulting from surgical intervention and those caused by cryptorchidism itself. Moreover, retrospectively, it is difficult to determine whether genuine cryptorchidism existed prior to surgery.

In this study an attempt was undertaken to correlate the biopsy findings of cryptorchid boys at the time of surgery with their present spermiogram and corresponding hormonal values. Moreover, the value of the biopsy taken during orchiopexy as a prognostic parameter for fertility outcome was also studied.

Patients

We studied twenty-four previously cryptorchid men aged between 17 4/12 and 25 years who had been operated upon in our clinic; 16 patients had had surgery for unilateral and 8 for bilateral cryptorchidism. 12 out of 16 unilateral patients had had unsuccessful HCG treatment prior to surgery. Successful unilateral descent occurred in three cases with bilateral cryptorchidism. Two out of 24 patients had an Ombrédanne orchiopexy while the remaining 22 were operated according to the Schoemaker technique.

Methods

General examination of the genitalia, penile length, as well as determination of the testicular volume according to the formula $\pi/6 \times D \times d^2$ [2] was performed. The volume of both testes was calculated together. Puberty rating was estimated according to Tanner [17]. Cubital venepuncture was performed and blood was taken for estimation of LH, FSH testosterone and estradiol. All hormones were estimated by RIA with the technique previously described [3]. Because a considerable number of the patients had to have their sperm specimen delivered by mail, only sperm volume, sperm count and sperm morphology were determinated in 19 out of 24 patients. All patients having a sperm count $< 20 \times 10^6$/ml had their spermiogram repeated. The patients were advised to refrain from sexual activities for at least three days before submitting their spermiograms to be examined. Testicular biopsies which were taken during surgery were fixed in glutaraldehyde (3%) postfixed in osmium-tetroxide and embedded in Epon according to the method already described [4]. The spermatogonia count in at least 50 tubuli seminiferi was determined. For statistical evaluation the Spearman rank correlation coefficient was used.

Results

All patients had Tanner stage V of pubertal development. The length of the stretched penis in the unilateral cryptorchid patients was $\bar{x}$ 11.7 cm (range: 9.5–13 cm) and for

Table 1. Unilateral cryptorchid patients

Age at surgery	Spermiogram age	S/T	Sperm-count x 10^6/ml	Sperm-volume (ml)	Percent of normal Sperm (%)	LH (IU/l)	FSH (IU/l)	Estradiol (pmol/l)	Testosterone (pmol/l)	Testis volume (cm^3)	Penis-length
14	19	0.25				8.3	3.4	46	16	38.24	11.5
13 8/12	20	0.67	88	4	73	10	2.4	90	21	54.12	10.5
11	22	0	35	1	55	10	5.4	76	18	34.97	12
8	19	0.31	28	1.5	62	9.4	3.2	140	29	51.51	12
8 6/12	19 8/12	0				10	2	78	32	60.86	10
10 7/12	21	0	1	6	20	12.5	15	53	17	31.90	10
9 9/12	19 6/12	0.04	12	2	71	10.8	5.9		26	21.18	10
12 11/12	23	0	42	5	70	10.1	5	59	23	69.03	13
8 11/12	19 6/12	1.78	93	1	49	5.8	2.9	63	11	70.47	10
10	18 4/12	0.84	30	2	66	7.3	3	45	19	29.42	13
7 10/12	22 4/12	0.16	67	2.5	60	15.1	2.1	60	8.5	71.60	9.5
10 6/12	20 7/12	0	20	2	18	15.1	5.7	40	16	32.95	11
13 9/12	19 3/12	1.3	41	5	70	8.7	2.1	100	28	34.25	13
7 10/12	21 5/12	0.06	1	0.5	20	10.4	8.6	80	19	24.71	10
14 10/12	21 10/12	0.04				12.5	3.6	90	33	36.54	10
7 3/12	22 9/12	0.07	23	1.5	64	13.4	4	51	19	44.58	10

Table 2. Bilateral cryptorchid patients

Age at surgery	Spermiogram age	S/T	Sperm-count x 10^6/ml	Sperm-volume (ml)	Percent of normal Sperm (%)	LH (IU/l)	FSH (IU/l)	Estradiol (pmol/l)	Testosterone (pmol/l)	Testis volume (cm^3)	Penis-length
11	21	0	0	1	0	17.6	15.1	76	20	16.74	10.5
9	19 4/12	0	2	1.5	47	14.3	23.6	62	15	26.14	15
11	21	0				15.7	10.2	56	12	31.90	11
13 2/12	20	0 bds	0	2	0	18.5	27.9	37	11	18.82	10
9 10/12	20	0	0	2.5	0	10.4	12.3	43	13	49.42	14
14 8/12	19	0.02	1	0.1	36	8.4	2.6	54	17	47.06	12
7	17 4/12	0.02				13	11.9	54	25	40.60	14
10	20	0.28	37	2	46	11.3	3.4	54	19	21.44	11

bilateral a median value of $\bar{x}$ 12.1 cm (range: 10–15 cm) was observed.

66% of unilateral cryptorchid patients (10/15) had a testicular volume lower than the normal population (58.56 ± 9 cm^3) [5], while 87% of bilateral cryptorchid patients also had a testicular volume lower than 1 SD of the normal population (Table 1, 2). No compensatory testicular hypertrophy was observed in our patient group (Table 1, 2).

Hormonal Data

LH (normal values 3–20 IU/l): The LH values of all cryptorchid patients were within the normal range (Table 1, 2).

FSH (normal values 2–6 IU/l): The plasma FSH values of 87% of the unilaterally cryptorchid patients and of 25% of the bilaterally cryptorchid patients were within the normal range (Table 1, 2). There was a significant correlation between LH and FSH ($p < 0.5\%$) plasma values (Table 3).

Testosterone (normal values 21.2 ± 6.6 nmol/l): The plasma testesterone values of 3.3% of the unilaterally and 37% of the bilaterally cryptorchid patients were lower than 1 SD of the normal data (Table 1, 2).

Estradiol (normal values 84 ± 25 pmol/l): 33% of the unilaterally and 75% of the bilaterally cryptorchid patients had lower than normal estradiol values in their plasma (Table 1, 2).

Table 3

Correlations	Spearman Rank Correlation Coefficient (two-sided significance level)	Correlations	Spearman Rank Correlation Coefficient (two-sided significance level)
S/T and sperm count	$p < 5\%$	S/T and estradiol	n.s.
S/T and LH	$-p < 5\%$	S/T and testosterone	n.s.
S/T and FSH	$-p < 5\%$	S/T and testicular volume	n.s.
S/T and normal sperm	$p < 5\%$	S/T and penis length	n.s.
LH and testis volume	$-p < 5\%$	LH and estradiol	n.s.
LH and FSH	$p < 5\%$	LH and testosterone	n.s.
FSH and testis volum	$-p < 5\%$	LH and penis length	n.s.
LH and normal sperm	$-p < 5\%$	FSH and estradiol	n.s.
FSH and normal sperm	$-p < 5\%$	FSH and testosterone	n.s.
Sperm count and normal sperm	$p < 5\%$	FSH and penis length	n.s.
Sperm count and LH	$-p < 5\%$	Sperm count and estradiol	n.s.
Sperm count and FSH	$-p < 5\%$	Sperm count and testosterone	n.s.
Sperm count and testicular volume	$p < 5\%$	Sperm and penis length	n.s.
Estradiol and testosterone	$p < 5\%$	Estradiol and testis volume	n.s.
Normal sperm and testosterone	$p < 5\%$	Estradiol and penis length	n.s.
		Testosterone and testis volume	n.s.
		Testosterone and penis length	n.s.
		Testis volume and penis length	n.s.

n.s. = not significant

Spermiogram

Four patients with unilateral cryptorchidism were found to have a sperm count $< 20 \times 10^6$/ml while 5 patients had a sperm count $> 40 \times 10^6$/ml (Table 1, 2). Six bilaterally cryptorchid patients were found to have a sperm count $< 20 \times 10^6$/ml while three of these were azoospermic. Not a single patient from the bilaterally cryptorchid group had more than $> 40 \times 10^6$/ml sperm count.

4/14 of the unilaterally cryptorchid patients and 50% of the bilaterally cryptorchid patients had a sperm volume lower than 2 ml (Table 1, 2). Only 25% of the unilaterally and none of the bilaterally cryptorchid patients had normal sperm morphology (normal values: > 70% normal forms).

When the number of the germ cells in the biopsy obtained at the time of surgery was correlated with the spermiogram a positive correlation was obtained (Table 3). Thus, those patients already having no germ cells in childhood in one or both gonads, had the lowest sperm count (Table 1, 2). A significant negative correlation was found to exist between S/T (spermatogonia count per tubule) and gonadotropins (Table 3). The sperm count was negatively correlated to LH, FSH and testicular volume (Table 3). There was also a negative correlation between testicular volume and LH as well as FSH indicating that the marked testicular atrophy was accompanied by high gonadotropin plasma values (Table 3). As expected, both testosterone and estradiol were significantly and positively correlated (Table 3). No correlation could be found between penile length and all other parameters (Table 3). Furthermore, no correlation was observed between testicular volume and S/T: testicular volume and estradiol nor testicular volume and testosterone (Table 3). Moreover, no correlation was found to exist between gonadotropins and estradiol and gonadotropins and testosterone (Table 3). Finally, no correlation could be found between S/T on the one hand and estradiol as well as testosterone on the other hand (Table 3).

Discussion

During their prepubertal period cryptorchid boys display insufficient gonadotropin levels with different degrees of expression (6, 7). Lower gonadotropin plasma values are found where gonadal damage is more pronounced [5, 12]. Furthermore, unilaterally cryptorchid boys lacking germ cells in their cryptorchid gonads also have a severely damaged contralteral descended testis [5]. This indicates that the same pathological mechanism is operating in unilaterally as well as in bilaterally cryptorchid boys. As Vermeulen has described [18] we also found that whenever LH levels were elevated FSH levels were increased, but more frequently pathological FSH values and normal LH values were observed. This suggests that in cryptorchid adults there is impaired Leydig cell function only when a serious impairment of tubular funtion exists [18]. Testicular damage is proportional to the degree of hypothalamo-pituitary-testicular axis insufficiency which had existed during the prepubertal period. Sizonenko et al. [16] observed that whereas basal FSH levels in both unilateral and bilateral prepubertal cryptorchid boys were normal, peak levels after LH-RH stimulation were significantly higher in prepubertal

bilateral cryptorchids than in either normal controls or unilateral cryptorchids. The authors interpreted this increase as due to tubular damage. However, Job et al. [12] and Cacciary et al. [1] as well as our group [5] were unable to confirm these results. The interpretation of this discrepancy may be explained by the findings of MacKellar et al. [14]. He recently reported an increase in the frequency of orchiopexy in boys 2–10 years of age which is more than twice what would have been expected according to the reported incidences at age one [14].

Several suggestions may be put forward:

1. The difficulty of differentiating retractile from true undescended testes.

2. Secondary cryptorchidism following apparent complete descent in infancy.

This second possibility is known to pediatricians and if previously normal testes with normal histology re-ascend, then an increase in FSH due to tubular damage may occur and would explain the findings of Sizonenko et al. [16]. Thus two populations in cryptorchid boys may exist. However, the vast majority (80%) of all cryptorchid boys have an impaired hypothalamo-pituitary-gonadal axis [5, 8].

As Lipschultz et al. [13] discovered, we also found that although the mean sperm density in cryptorchid men was only one-third of that of the normal population, the serum testosterone level did not differ significantly from that of the control group. Patients treated in childhood for cryptorchidism with orchiectomy had the same rate of subnormal sperm density as those who still retained their unilateral undescended testis [19]. This makes production of a harmful substance by the undescended testis to its contralateral descended partner less likely.

The positive correlation between the biopsy findings and sperm count suggests that the biopsy obtained during childhood has a prognostic value. Moreover, the fact that 7 out of 1,331 cryptorchid boys had carcinoma in situ cells in their gonads underlines the importance of performing testicular biopsy [8]. Therefore, obtaining testicular biopsies in cryptorchid boys because of their prognostic values and the possibility to discover carcinoma in situ cells is highly recommended, particularly because it has been shown that performing small testicular biopsy in childhood during orchiopexy has no adverse effect on the testis [11]. Finally if the semi-thin sections for analysing the testicular biopsy are used, it is possible to distinguish between true cryptorchid testes and retractile testes which have normal histology and normal fertility chances, giving the surgeon verification of the correct diagnosis [9].

Moreover, since it is possible to stimulate germ cells to divide and increase their number, it is even more important to perform a biopsy to influence the unfavourable fertility prognosis in at least 30–40% of all cryptorchid boys [10].

References

1. Cacciari E, Cicognani A, Pirazzoli P, Zappola F, Tassoni P, Bernardi F, Salardi S (1976) Hypophysogonadal function in the cryptorchid children. Difference between unilateral and bilateral cryptorchidism. Acta Endocrinol (Copenh) 83:182
2. Daniel Jr WA, Feinstein RA, Howard-Peebles P, Baxley WD (1982) Clinical and laboratory observations. Testicular volumes of adolescents. J Pediatr 101:1010
3. Hadžiselimović F, Girard J (1977) Pathogenesis of cryptorchidism. Horm Res 8:76
4. Hadžiselimović F (1977) Cryptorchidism. Adv Anat Embryol Cell Biol 53/3
5. Hadžiselimović F (1983) Cryptorchidism, management and implications. Springer, Berlin Heidelberg New York
6. Hadžiselimović F, Girard J, Herzog B (1979) Lack of germ cells and endocrinology in cryptorchid boys from one to six years of life. In: Bierich JR, Giarola A (eds) Cryptorchidism. Academic Press, London New York, p 129
7. Hadžiselimović F, Girard J, Herzog B (1977) Treatment of cryptorchidism by synthetic luteinising-hormone-releasing hormone. Lancet II:1125
8. Hadžiselimović F (1983) Cryptorchidism: when to treat? In: Forum d'Andrologie Hôpital Saint Antoine. Paris 25 juin 1983, Expansion Scientifique Française
9. Hadžiselimović F, Herzog B, Girard J, Stalder G (1984) Cryptorchidism – histology, fertility and treatment. Prog Reprod Biol Med 10:24
10. Hadžiselimović F (1982) Pathogenesis of undescended testis. Eur J Pediatr 139:255
11. Hjort T, Linnet L, Skakkeback NE (1982) Testicular biopsy: indications and complications. Eur J Pediatr 138:23
12. Job C, Garnier PhE, Chaussain JL, Toubland JE, Canlorbe P (1974) Effect of synthetic luteinizing hormone-releasing hormone on the release of gonadotropins in hypophyso-gonadal disorders of children and adolescents. IV. Undescended testes. J Pediatr 84:371
13. Lipschultz LI, Caminos-Torres R, Greenspan BA, Snyder PJ (1976) Testicular function after orchidopexy for unilaterally undescended testis. N Engl J Med 295:15
14. MacKellar A, Lugg MM, Keogh EJ (1984) The undescended testis lies, damned lies and statistics. Prog Reprod Biol Med 10: 24
15. Scorer CG (1964) The descent of the testis. Arch Dis Child 39: 605
16. Sizonenko CP, Schindler AM, Cuendet A (1981) Clinical evaluation and management of testicular disorders before puberty. In: Burger H, Kretser D de (eds) The testis. Raven Press, New York
17. Tanner JM (1962) Growth at adolescence. Blackwell Scientific Publications, 2nd ed
18. Vermeulen A, Comhaire F, Coutent G, Rubens R (1979) Consideration concerning the function of hypothalamo-pituitary-gonadal axis in cryptorchidism. In: Bierich JR, Giarola A (eds) Cryptorchidism. Academic Press, London New York, p 305
19. Woodhead DM, Pohl DR, Johnston DE (1973) Fertility of patients with solitary testes. J Urol 109:66

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