A cross-sectional study of cryptorchidism in children: testicular volume and hormonal function at 18 years of age

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ABSTRACT

Purpose: To evaluate the relationship between unilateral or bilateral cryptorchidism, patient age, primary location of the gonad and modality of treatment with testicular volume and hormonal status at 18 years in patients diagnosed and treated for cryptorchidism during childhood.

Materials and Methods: Testicular volume, LH, FSH, and testosterone were evaluated in 143 young men at 18 years treated for unilateral (n=103) or bilateral (n=40) cryptorchidism.

Results: Unilateral cryptorchidism: Location of testis was prescrotal in 36 patients, inguinal in 52 and non-palpable in 15. The mean volume was 9.7 mL compared to 16.2 mL for the spontaneously descended testicle in unilateral cryptorchidism. However, 22 patients who received HCG had a significantly bigger testis (11.8 mL) than those treated with primary surgery (9.2 mL). The results showed a significant positive correlation between testicular volume and patient age at treatment.

Bilateral cryptorchidism: Location of testis was prescrotal in 34 cases, inguinal in 40 and 6 patients with non-palpable testicles. Mean volume at 18 years was 12.9 mL, greater than unilateral cryptorchid testis (9.7 mL) but smaller than healthy contralateral in unilateral cases (16.2 mL). There were significant differences in the testicular growth for bilateral patients with testicular descent after being treated with HCG (14.4 mL) in respect with those untreated (11.1 mL) or those who underwent primary surgery (11.4 mL). There was a significant positive correlation between the testicular volume and palpable (12.4 mL) or non-palpable testis (10.4 mL). There was a correlation between unilateral or bilateral cryptorchidism and levels of FSH.

Conclusions: Testicular volume and hormonal function at 18 years for patients diagnosed and treated for cryptorchidism during childhood are strongly influenced by whether the undescended testis was unilateral or bilateral. Location of the testes at diagnosis or age of initial treatment exerts no definite effect on testicular volume improvement or hormonal levels at 18 years of age.

INTRODUCTION

Incomplete descent of one or both testicles from the abdominal cavity, through the inguinal canal into the scrotum (cryptorchidism) is a multifactorial etiology abnormality that affects 1-1.8% of male infants (1). It is reported to be associated with infertility and testicular cancer (2). To minimize these complications is mandatory the placement and fixation of the testis in
the scrotum (2, 3). It is not known the ideal age for surgical treatment and which is the ideal therapy (4). However, based on several studies that show that undescended testes undergo early and progressive deterioration, the recommended age for treatment has been decreasing gradually as we have improved our understanding of spermatogenesis (3, 5).

Testicular damage may be secondary to the abnormal position of the testis. This damage is basically characterized by a progressive reduction in germ cell number and size of the seminiferous tubules with peritubular fibrosis and hyalinization, resulting in a decrease of the number of Leydig cells. These facts may affect the production of sexual hormones promoting testicular atrophy with subsequent infertility (6-8). Hence, the testicular volume and hormone levels are related to reflect the spermatogenesis and are considered to be indirect indicators to predict the potential for fertility. (9-11). But it is also possible that the undescended testis has been inherently atrophic (12-14); therefore, early correction of cryptorchidism would be less important (15-17).

A cross-sectional observational transverse study was performed to evaluate the relationship between age at treatment, location of the gonad and type of treatment (hormonal and/or surgical therapy) on testicular growth and hormonal function at 18 years of age in patients treated for unilateral or bilateral cryptorchidism during childhood. To the best of our knowledge, this is the first reported survey of longitudinal long-term follow-up of patients with cryptorchidism.

PATIENTS AND METHODS

Study population
The study population consisted of 143 boys who were born before 1993 and were diagnosed as having unilateral (103 cases) or bilateral (40 patients) primary cryptorchidism. Patients with retractile testis, endocrine diseases, chromosomal abnormalities, incomplete data or dysmorphic features were excluded from the study. The mean age at effective treatment was 7.42±3 years. All these patients were evaluated at 18 years of age and divided in two separate groups: unilateral and bilateral cases.

DESIGN OF THE STUDY AND FOLLOW-UP DATA

Design of study
A cross-sectional observational transverse study at 18 years of age of boys diagnosed and treated of unilateral or bilateral cryptorchidism during infancy and/or childhood period.

Physical examination
Physical examination included assessment of testis position obtained by gentle manipulation. Testis position was classified as pre-scrotal (between external inguinal ring and scrotum), inguinal, or nonpalpable. Testicular volume was measured using a Prader orchidometer (a chain with 13 numbered beads of increasing size from 1 to 30 mL).

Testicular ultrasound
After the physical examination, testicular volume was measured with ultrasonography at 18 years of age. All ultrasound examinations were performed with a 12-MHz linear transducer. To measure the testicular volume, the scanner was placed on the inguinal region or on the scrotum. Three separate transverse and longitudinal images were recorded for each testis to assess the volume. After maximum length, width and height were obtained in the ultrasound, the testicular volume was calculated using the empirical formula of Lambert first described in 1951. The Lambert equation \( \text{length} \times \text{width} \times \text{height} \times 0.71 \) estimates the ellipsoid testicular volume more accurately. The testicular volume estimated by Prader orchidometry correlated closely with the measurements by ultrasonography (18).

Surgical and/or hormonal therapy
According to the protocol established in our hospital, hormonal therapy was offered to all cases as first line treatment. Boys who accepted were given human chorionic gonadotropin hormone (HCG) intramuscularly twice a week for five weeks. Each injection was 250 IU for children under two years, 500 IU. for children between 2 and 6 years, and 1,000 IU for ages 6 to 11 years, following the recommendations of the expert group of WHO in cryptorchidism (19). Patients
who refused or did not respond to hormonal treatment, underwent surgery for correction of undescended testes according to the standard surgical orchidopexy technique (20). Effective age of treatment was considered once the testis was definitely located in the scrotum after hormonal and/or surgery.

Follow-up
All patients were followed at the outpatient clinic in the first year at one, 3, 6 and 9 months after treatment (medical or surgical). Then, they were reviewed annually until age 18. At the age of 18, a physical examination was performed in all patients, checking the location of the testes and their size using a Prader orchidometer. True testicular volume was determined by ultrasonography and the empiric formula of Lambert. One pediatric surgeon (RVC) performed more than 95% of the clinical examinations. Blood samples were analyzed in all adolescents for FSH, LH and Testosterone levels. Hormonal levels were measured using an immunometric monoclonal assay. Semen analysis was realized only in a small number of adolescent’s patients who voluntarily provided a semen specimen after ejaculation. Patients were definitely discharged once informed of the laboratory results and concerns about potential of fertility and risk of testicular malignancies.

Statistical analysis
The mean, median, and range were calculated using standard methodology. Data were reported as means when normally distributed, and medians when non-normally distributed. Categorical variables are presented as absolute numbers and percentages, continuous variables as means, standard deviations, minimum and maximum range. Means were compared using the chi-squared or Fisher exact test and medians were compared using the non-parametric Mann-Whitney U test. Differences in proportions among categoric data were assessed using the Fisher exact test. All data were analysed by the statistical package SPSS for Windows, version 18.0 (SPSS, Chicago, IL, USA). Statistical significance was set at p<0.05.

ETHICAL APPROVAL
The Local Ethical Committee of the University Hospital of Santiago de Compostela, Spain approved the study. Informed consent was obtained from all parents of the patients who agreed to participate in the study.

RESULTS
The mean age at referral for undescended testis was 7.42 years (range 1-13). Of the 143 boys diagnosed with undescended testis, the anomaly was bilateral in 40 and unilateral in the remaining 103. Of these 103 boys, the anomaly was on the left in 45 (43.7%) and on the right side in the remaining 58 (56.3%). In all cases the testicular volume was measured by Prader orchidometry and ultrasonography.

Unilateral Cases
Among unilateral cases (Table-1) only 15 patients had non-palpable testis (14.5%) and 88 had a palpable gonad. Of these 103 unilateral patients, 26 patients refused hormone treatment. Treatment with HCG induced the descent in 22 testes (28.6%) for a total of 77 patients. The descent of those located in the inguinal region was 3/39 (7.7%) and 19/32 (59.4%) of those located high scrotal. Unilateral non-palpable testis in patients who received HCG therapy did not respond (0/5). We performed an orchidopexy in 81 patients with unilateral disease, 26 primary and 55 subsequent to failure of medical treatment. In 20% (3/15) of non-palpable unilateral cases, a very atrophic testicle was found during the surgical procedure. The volume of undescended testicle in unilateral cases was significantly smaller in size (median 9.7 mL) than its counterpart normal testicle (median 16.2 mL). The hormone levels were within normal ranges in all cases, mean 4.01 IU/L for FSH, 4.32 IU/L for LH and 6.75 ng/mL for testosterone. Testicular volume of patients with scrotal descent after HCG treatment (22 cases) was significantly higher (mean 11.8 mL) in respect to those who were operated after failure of hormonal therapy (mean 9.2 mL) and those who underwent primary surgery (mean 8.6 mL).
(p=0.019). However, hormone levels were similar in all groups without any statistically significant differences.

In this survey, testicular volume of the palpable testes was significantly greater than non-palpable ones (mean 11.0 mL vs. 7.6 mL). However, volume of the contralateral testes was significantly lower in the group of palpable testes. Thus, the total testicular volume (ie, sum of the volumes of both testes estimated by Lambert’s equation or Prader orchidometry) in both groups of patients related to unilateral cryptorchidism (palpable and non-palpable) was similar. In patients with retained testicles in the inguinal position, the volume was significantly lower in respect to its counterpart, regardless of type of treatment. No differences in hormone levels according to the situation of the gonad were noticed (Table-1). In boys treated before 2 years of age (Table-2) there was a further development of both the undescended testicle (median 13.4 mL) and healthy scrotal counterpart (median 17.1 mL) in respect to the patients treated after 2 years of age (11.0 mL and 14.7 mL respectively). However, FSH, LH and testosterone levels did not show statistically significant differences in these two groups of patients.

Bilateral Cases

In patients with bilateral cryptorchidism (Table-3) 6 cases had non-palpable testes but 74 had palpable ones. Of all bilateral cases, 5 pa-
Table 2 - Unilateral cryptorchidism (n=103) Features based on age and therapy (A-only hormonal treatment; B-hormonal first and surgery later; CX – surgery alone; TEST-Testosterone).

|                | < 2 years |          | 2-6 years |          | > 6 years |          |
|----------------|-----------|----------|-----------|----------|-----------|----------|
|                | Hormonal therapy | CX | Hormonal therapy | CX | Hormonal therapy | CX |
|                | A   | B   | A   | B   | A   | B   |
| FSH (UI/L)     | 4.0 (*) | 3.5 | 5.3 (*) | 3.5 | 4.0 | 3.8 |
| Range          | (2.5-5.4) |     | (1.1-7.0) |     | (2.0-9.5) |     |
| LH (UI/L)      | 2.8 (*) | 4.2 | 2.7 (*) | 4.8 | 3.1 | 3.8 |
| Range          | (3.3-5.6) |     | (2.9-5.9) |     | (3.2-6.1) |     |
| TEST (Ng/mL)   | 4.9 (*) | 7.5 | 5.6 (*) | 5.9 | 4.6 | 5.9 |
| Range          | (5.5-16.6) |    | (3.8-6.6) |    | (4.8-10.1) |    |
| Age at treatment | 11.9 | 18.3 | 17.8 | 36.0 | 96.2 | 80.9 |
| (months)       | (8.6-15.7) | (14.5-21.3) | (17.3-20.1) | (28.5-59) | (46.3-126) | (87.6-142) |
| Testic. Volume |          |          |          |          |          |          |
| Affected testis | 17.2 | 11.2 | 11.9 | 15.4 | 8.3*** | 11.2 |
| (11.4-23.0) | (9.3-13.5) | (0.1-15.0) | (11.6-18.1) | (6.5-11.1) | (7.1-12.4) | (8.9-15.8) |
| Non-affected testis | 18.5 | 15.0 | 17.9 | 15.3 | 16.7 | 14.0 |
| (18.0-19.0) | (12.1-17.5) | (12.3-33.2) | (13.4-20.1) | (11.2-18) | (10.6-21.6) | (11-19.9) |
| Patients       | 2   | 5   | 3   | 4   | 20  | 4   |
|                | 16  | 30  | 19  |          |          |          |

(*) Only 1 case with data
* p < 0.05; ** p <0.01; *** p < 0.005; **** P <0.0001

The mean volume of the 14 testes that descended after treatment with HCG (14.4 mL) was significantly greater than the non-responders group (11.1 mL) or even than the group of patients who underwent orchidopexy without previous hormonal therapy (11.4 mL). A significant reduction in testicular size was noticed in cases of non-palpable bilateral testes (10.4 mL) in respect to palpable ones (12.4 mL). In these particular patients with bilateral cryptorchidism and non-palpable testes, the FSH levels were significantly lower in relation to palpable cases (15.6 vs 10.4 IU/L). Similar results were obtained with LH levels (6.7 vs 4.4 IU/L) and Testosterone values (3.7 vs 6.1 ng/mL).

In patients with bilateral cryptorchidism treated before two years of age, we noticed mean testicular volume measurements significantly smaller (10.3 mL) than those treated after two years (12.1 mL). Comparing these two separate
Table 3 - Bilateral cryptorchidism (n=80) Features based on testis location and therapy used (A-only hormonal treatment; B-hormonal first and surgery later; CX – surgery alone).

|                      | Pre-Scrotal (34) | Inguinal (40) | Non-Palpable (6) |
|----------------------|-----------------|----------------|-----------------|
|                      | Hormonal Therapy | CX | Hormonal Therapy | CX | Treatment |
|                      | A               | B | A | B | |
| Patients             | 12              | 19 | 3 | 2 | 31 | 7 | 6 |
| FSH (UI/L)           | 9.2             | 6.6 | 13.9 | - | 5.3 | 17.1 | 15.6 |
| Range                | (3.0-10.8)      | (3.5-10.1) | (13.9-22.3) | (2.3-13.2) | (7.5-19.7) | (15.6-15.6) |
| LH (UI/L)            | 4.2             | 3.4 | 4.0 | - | 4.8 | 5.9 | 6.7 |
| Range                | (3.1-9.6)       | (2.5-4.9) | (4.0-5.9) | (3.4-7.7) | (4.8-8.8) | (6.7-6.7) |
| TEST. (Ng/mL)        | 7.5             | 5.6 | 5.9 (*) | - | 5.7 | 6.0 | 3.7 |
| Range                | (6.0-8.4)       | (5.3-6.4) | (5.3-6.6) | (2.5-8.5) | (3.7-3.7) |
| Age at Treat. (Months) | 96.3           | 109.1 | 114.0 | 29.6 | 82.9 | 100.2 | 55.5 |
|                      | (71.8-102.5)    | (61.0-125.7) | (88.6-115.0) | (29.6-29.6) | (30.6-130.0) | (37.1-103.0) | (47.8-127.9) |
| Testic. Volume       | 15.40           | 12.6 | 11.2 | 13.5 | 10.3 | 11.7 | 10.4 |
| Range                | (10.9-16.7)     | (9.0-18.5) | (10.5-12.0) | (12-15.0) | (7.6-14.7) | (5.1-13.1) | (1.8-18.1) |

(*) Only 1 case with data.

groups of bilateral cases (treated before and after two years of age), hormonal levels were significantly different too: FSH (3.0 vs 9.0 IU/L), LH (5.1 vs 5.5 IU/L) and Testosterone (6.5 vs 6.0 ngr/mL) (Table-4). Statistical analysis results indicated that the mean volume of undescended testicle showed a strong positive relationship with type of cryptorchidism (unilateral or bilateral). Testicular volume is smaller in unilateral cryptorchidism; however, total testicular volumen is greater in unilateral cases in relation to bilateral patients due to the compensatory effect of the healthy contralateral one. Accurate determination of hormonal levels at 18 years of age in our study also showed a significant elevation of FSH levels in bilateral cryptorchidism (p=0.001), with slight increase in LH levels. Testosterone values were significantly lower in bilateral patients in relation to unilateral cases. There was statistically significant difference between the two groups.

**DISCUSSION**

Since testicular volume plays a definitive role in potential of fertility in young adults, accurate measurement is supposed to be relevant in the follow-up of cryptorchid patients. Testicular volume in otherwise healthy young adults is approximated 18-20 mL (10, 21). Hypoplasia is considered in those with volume less than 14 mL (22, 23) or those with a difference greater than 3 mL in relation to the healthy contrateral (24). Volume loss was shown to have progressive deleterious effects on the future fertility status. The minimum testicular size for good fertility is approximately 12 mL (22). Total testicular volume (ie, sum of the volumes of both testes) of approximately 30 mL is indicative of normal testicular function. We consider that an accepted normal testicular volume at 18 years of age is 14-16 mL (22, 24). Since approximately 70%-80% of tes-
ticular mass consists of seminiferous tubules, testicular volume is largely a reflection of spermatogenesis (23, 25-27). The testicular volume has been one of the most important endpoints predicting the outcomes of cryptorchid patients related to spermatogenesis. Since it is not usually possible to perform semen analysis in pediatric age group and established clinical criteria to properly define the favourable outcomes are absent, the improvement in the testicular volume has been considered to be the most relevant indirect measure for potential of fertility in adolescents patients (28, 29).

Vast majority of authors reported a significant decrease in testicular volume in cryptorchid patients (10, 24, 30-33), more evident in high locations (30) and in patients treated later during childhood (33). However its not clear if age at referral of hormonal therapy can achieve an improvement in testicular size (33, 34, 36-38).

According with other authors (39, 40) our results showed a marked decrease in the volume of the cryptorchid testis related to the healthy contralateral in unilateral cases. Our rate of testicular volume loss in respect to healthy contralateral in unilateral cases is 34.76% and in bilateral patients is 23%; both are similar of the percentages refered by other studies (24). Although we have used the contralateral healthy testis as a control, it would be interesting for future studies to include a real control group of normal age-matched adults to compare both hormone levels and testicular volume.

Since the location of the testicle before treatment is strongly related to the ipsilateral testicular volume catch-up growth rate at 18 years of age, our results showing an improvement in size after hormonal therapy on both unilateral and bilateral groups are consistent with those reflected in the reviewed literature due to the more caudal location of these testes (3). This volume catch-up growth rate depends on location before treatment but is not related to the type of therapy employed. Likewise, the lower catch-up growth rate of non-palpable testis at 18 years of age may be explained by the high location inherent to these testicles, and is

| AGE       | < 2 years | 2 - 6 years | > 6 years |          |          |
|-----------|-----------|-------------|-----------|----------|----------|
|           | Treatment | Treatment   | CX        | Treatment | Treatment |
|           | B         | A           | B         | A        | B        |
| FSH (UI/L)| 3.7       | 2.8         | 9.5       | -        | 10.6     | 6.6       | 15.5      |
| Range     | (1.9-6.3) | (2.5-3.2)   | (5.0-15.6)|          | (9.2-11.3)| (3.5-11.3)| (9.1-21.0) |
| LH (UI/L) | 5.1       | 10.4        | 4.6       | -        | 3.3      | 3.8       | 5.3        |
| Range     | (4.3-5.7) | (4.2-16.7)  | (2.7-7.2) |          | (2.4-7.2)| (2.8-7.9)| (4.2-8.1)  |
| TEST. (Ng/mL) | 6.5 | 6.1         | 5.4       | 5.9 (*)  | 7.5      | 5.6       | 5.8        |
| Range     | (4.0-6.6) | (4.4-7.9)   | (4.1-6.3) |          | (6.6-9.8)| (5.3-5.9)| (2.5-8.5)  |
| Age at Treat. | 20.4 | 43.7        | 47.4      | 37.0     | 100.5    | 119.5     | 101.6      |
| (Months)  | (16.1-23.4)| (29.6-71.8)| (33.6-61.0)| (36.9-37.2)| (95.3-111.3)| (92.4-139.8)| (91.5-112.2)|
| Testic Volume | 10.3 | 15.0        | 10.3      | 6.6      | 13.9     | 12.1      | 14.5       |
| Range     | (7.4-18.9)| (12.4-16.1)| (6.6-19.6)| (1.2-12.1)| (10.0-17.2)| (8.8-15.4)| (6.7-12.8) |
| Patients  | 7         | 6           | 15        | 2        | 8        | 34        | 8          |

(*) Only 1 case with data
non-related to the treatment modality. However, in unilateral cryptorchidism there is a remarkable improvement in the contralateral testis growth and there are no differences in the total testicular volume in relation to the bilateral group.

However, some authors underestimated the correlation of testicular volume with sperm count of semen profiles (41). According with others, we think that testicular volume had the strongest positive correlation with sperm density, followed in decreasing order by total sperm count per ejaculate, total motile sperm count per ejaculate, and percentage of motile sperm (24).

Likewise, the benefit of early treatment or adjuvant hormonal treatment does not seem clear (10, 42, 43). Our study showed that in patients with unilateral cryptorchidism treated before 2 years of age, testicular growth was markedly higher for both the undescended testis and the healthy contralateral, compared with those treated after 2 years of age. In bilateral cryptorchidism, by contrast, there is a decrease in catch-up growth testicular rate in the group of patients treated early. Furthermore, these growth differences do not reflect changes in hormone levels at 18 years of age in both age groups (treated before and after two years). Nevertheless, the small number of cases treated before two years of age may influence our statistics workup. Anyway, in the group of patients with unilateral criporchioresism, the early treatment (before two years of age) had a markedly improvement in testicular growth in relation to those treated later. Although animal studies have confirmed the positive effect of early orchiopexy in bilateral cryptorchidism and the little benefit of additional hormone therapy (44), we didn’t find these results in our series.

One of the relevant findings of our study is that hormonal treatment before surgery does not appear to exert any beneficial effect in testicular growth at 18 years of age. There are no significant differences in catch-up growth testicular rate and hormone levels between patients undergoing primary surgery and those who were operated on after hormonal treatment failure. We found a significant improvement in testicular size in patients whose testes descended with HCG treatment alone.

Some authors have reported a weak correlation between testicular size at orchiopexy, and lower ratios of paternity, hormone levels, sperm count and testicular volume in adult patients (45, 46). According with others, we found a strong positive correlation between lower FSH levels (a marker of spermatogenesis) and high location of the testicle (9, 47, 48).

We didn’t find a direct relationship between testicular volume of the undescended testes and hormone levels in patients at 18 years of age. However, we noticed that in bilateral cryptorchidism, FSH levels were significantly higher than in unilateral patients, despite having the larger volume of the healthy contralateral testes and equal total testicular volume. A possible explanation theory is that there are embryologic and etiopathogenic differences between the unilateral and bilateral criprorchidism (49-51). Anyway, what seems evident is that with only one testicle located in scrotum, the potential of fertility may be preserved (52).

CONCLUSIONS

In conclusion, the current study shows that the testicular volume and hormonal function at 18 years of age for patients diagnosed and treated for cryptorchidism during childhood are positively and strongly influenced by whether the undescended testis was unilateral or bilateral. Location of the testes at diagnosis or age of initial treatment exerts no definite effect on testicular volume improvement or hormonal levels at 18 years of age.

CONFLICT OF INTEREST

None declared.

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