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CRYPTORCHIDISM – OUR RESULTS AND TREATMENT PROTOCOL

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We analyzed patients operated on for cryptorchidism at the Pediatric Surgery Department during a 2-year period (2008-2009). We analyzed patient age, side of cryptorchidism, position of the testes, operative approach (open, laparoscopic), type of operative treatment (orchydopexy, orchydectomy with implantation of testicular prosthesis), and results of histopathologic analysis of testes that underwent biopsy. During the study period, 192 patients, mean age 5.62±3.78 years, underwent surgery for cryptorchidism. Unilateral cryptorchidism was present in 161 (83.9%) patients, 93 (57.8%) of them right-sided. A total of 223 testes underwent surgery, 22 (9.9%) of these in prescrotal position, 174 (78%) in inguinal position and 27 (12.1%) in intra-abdominal position. Laparoscopic exploration was performed in 37, orchydopexy in 27 and resection of testicular remnant with immediate implantation of testicular prosthesis in the remaining 10 patients. Intraoperative biopsy was done in 165 (74%) testes. Despite continuous education, the mean patient age of 5.62 years at the time of treatment was above the desired age of two years. It is commendable that an increasing number of patients undergo biopsy during orchydopexy.

Descriptors: CRYPTORCHIDISM - surgery; CLINICAL PROTOCOLS; BIOPSY; CHILD; CHILD, PRESCHOOL

INTRODUCTION

Undescended testis is one of the most common anomalies of the urogenital system, occurring in about 3.4% of male babies born at term, and in about 30% of prematurely born male babies (1). Given its frequency, and despite the presence and understanding of this problem for a long time, cryptorchidism still remains a great therapeutic challenge. Undescended testis can cause serious problems such as infertility, increased incidence of testicular cancer, predisposition to testicular torsion and psychosexual problems (2).

Currently there is a consensus in the literature that treatment of undescended testis should be completed by the end of the second year of age because spontaneous descensus after that age (even after the 6th month of age according to some authors (3)) is highly unlikely (4, 5), and more importantly because the number of germ cells in the undescended testis after that age decreases drastically (5).

There are two therapeutic approaches: one is surgical, when it is assumed that the pathophysiologic etiology of cryptorchidism is an anatomical abnormality; and hormonal treatment, when cryptorchidism is observed as an endocrine disorder. Trend in the modern treatment of undescended testis is to use both operative and hormonal treatment in order to achieve optimal results.

It is known that about 33% of patients with unilateral cryptorchidism have problems with fertility in the adult age, while 66% of patients with bilateral undescended testes can expect problems with fertility in adulthood (5). Until recently, it was almost impossible to give a prediction if a patient with cryptorchidism will have problems with fertility later, in adulthood. Discovery of the importance of Ad spermatogonia has made this prediction very easy. What is more important, there are published data that indicate that even those patients without Ad spermatogonia (and consequently poor prognosis for future fertility) may be helped with postoperative hormonal therapy (6).

This treatment protocol (operative treatment followed by postoperative hormonal therapy) was introduced in clinical practice at our hospital in 2007. We wanted to determine how many patients with undescended testis were treated this way at our hospital over the past two years (2008-2009), since it is well known that new procedures are not easily accepted among all physicians, as well as to analyze all relevant parameters regarding patients with cryptorchidism at our hospital (patient age, the side of undescended testis, surgical approach and treatment option, and histopathology results).

MATERIAL AND METHOD

Analysis included all patients hospitalized at the Pediatric Surgery Department in Novi Sad during a two-year period (2008-2009) under the diagnosis of undescended testis. In order for the patient to be hospitalized at the Pediatric Surgery Department, he must have been examined at least two times by a pediatric surgeon, in appropriate conditions (calm child, warm examination room and warm hand of the examiner), and every possibil-

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ity of a migrating testis should have been excluded. We noted the age of the patients, the side of undescended testis, intraoperative position of the testis (prescrotal, inguinal or intra-abdominal), type of operative treatment (laparoscopic or open), type of surgery (orchiopexy or orchiectomy with implantation of prosthesis), number of patients submitted to testicular biopsy intraoperatively, and finally the results of histopathologic analysis.

The study was approved by the Ethics Committee of the Institute for Child and Youth Health Care.

Biopsy was obtained in all patients with a diagnosis of undescended testis who underwent surgery performed by one of our pediatric urologists. Patients who were operated on by general pediatric surgeons did not undergo biopsy.

Biopsy is taken after preparation of funicular elements, from the upper pole of the testis in close proximity of epididymis. A transverse incision is made on *tunica albuginea*; a total length of 4 mm testicular tissue is pressed out and approximately 1 mm^3 of tissue is taken for analysis. Tissue is then, without any contact with gauze or gloves, placed in cold 2% glutaraldehyde. *Tunica albuginea* is closed with interrupted sutures.

Biopsies were fixed in 2% glutaraldehyde in a phosphate buffer, post-fixed in osmium-tetroxyde, embedded in EPON and sectioned at 0.5-1.0 mL. Histologic sections were stained with toluidine blue and examined by light microscopy. The number of complete tubules in the entire biopsy was estimated (≥50 tubules). The spermatogonia were counted and expressed as the number of spermatogonia *per* tubule (S/T). Ad spermatogonia were defined as spermatogonia with a „hole“ in the center of the cell nucleus. The presence or absence of Ad spermatogonia was noted for each of the patients (Figure 1).

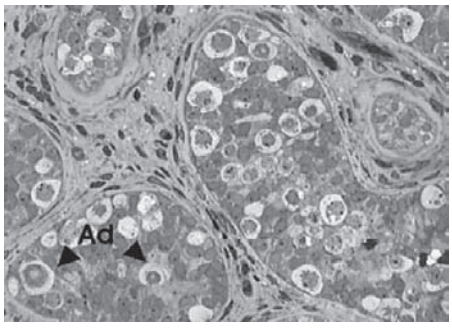

Figure 1. *Ad spermatogonia*

RESULTS

During 2008 and 2009, a total of 192 patients underwent surgery for undescended testes. The mean age of the patients was 5.62±3.78 years. Unilaterally undescended testis was operated in 161 (83.9%) patients, 93 of them for right undescended testis (57.8%) (Figure 2).

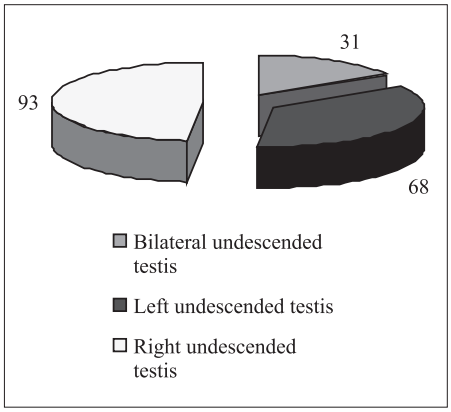

Figure 2. *Distribution of undescended testes according to side*

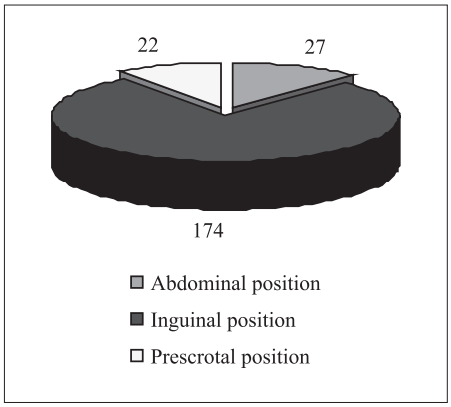

Figure 3. *Intraoperative position of the testis*

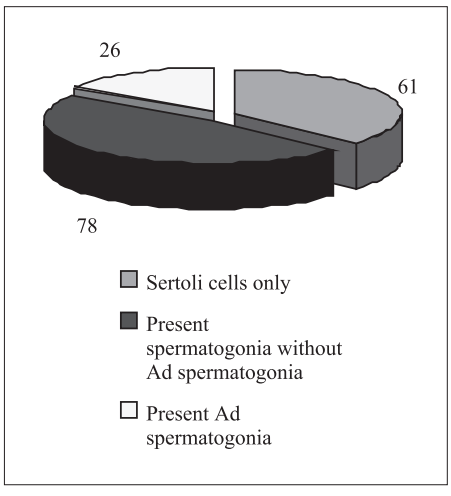

Figure 4. *Histopathologic findings*

Out of the total number of operated testes (n=223), 22 (9.9%) were in prescrotal position, 174 (78%) in inguinal position, and 27 (12.1%) in intra-abdominal position (Figure 3).

Laparoscopic exploration was performed in 37 patients. In 27 patients, an orchydopexy was performed in 27 patients, whereas the rest of ten patients underwent testicular remnant resection and implantation of testicular prosthesis. Out of the total number of operated testes, 165 (74.0%) underwent mini-biopsy. Sertoli cells only were found in 61 (37.0%) testes, 78 testes had spermatogonia but without Ad spermatogonia, while only 26 (15.7%) testes had normal histology (with both Ap and Ad spermatogonia) (Figure 4).

DISCUSSION

Cryptorchid testis can be easily recognized under the microscope even under small magnification. It is characterized by wide, empty intercellular space on the one hand, and small seminiferous tubules with a reduced number of germ cells on the other. Two pathognomonic characteristics of undescended testes are circular tubules with spherical hole in the center and secondary regions with completely degenerated tubules (5). In healthy male patients, the number of spermatogonia increases throughout the childhood. At the end of puberty, each testis has approximately 800,000,000 spermatogonia (7).

Over the first six months of life, the number of spermatogonia in the testes of patients with undescended testes is within the normal range (8-10). Besides fetal spermatogonia, which are structurally identical to fetal spermatogonia in healthy testes, a reduced number of all other types of spermatogonia (Ap and Ad) can be found in undescended testes.

Already after the second year of life, up to 22% of patients with unilateral undescended testes will have no spermatogonia in their testes (5). Besides quantitative changes, there are qualitative changes as well. The number of binuclear spermatogonia increases. Spermatogonia are mostly fetal, sometimes with a bizarre nuclear structure. Histometric analysis shows a change in the cytoplasm-nucleus ratio in favor of the nucleus (6). The development of germ cells in general is deterred.

At the age of 6, the number of fetal, transitory and Ap spermatogonia is de-

creased, and most of them show signs of incipient degeneration. Ad spermatogonia and primary spermatocytes are almost never found.

Not only are germ cells affected. Leydig cells are affected as well. The number of Leydig cells is lower compared to normal testes, and their progressive degeneration starts at the age of 5 (11).

It is well known that the testes that remain undescended in puberty will result in sterility in adulthood (12). However, a number of patients treated before puberty for unilateral or bilateral undescended testes will also have problems with fertility. It is estimated that approximately 25% of patients with unilateral undescended testes and 50% of patients with bilateral undescended testes will be infertile despite successful orchiopexy performed before puberty (5).

A number of factors have been found to affect future fertility: the age of the patient at the time of treatment, type of therapy, and initial position of the testis. Several studies have shown that an early treatment of undescended testis is favorable for future fertility (13). It has also been determined that the introduction of hormonal therapy into the treatment protocol has also a favorable effect on future fertility (5). Intra-abdominal position of the undescended testis has been associated with poor prognosis (5).

There is a definite correlation between testicular histology of the patients with undescended testes and spermiograms of the same patients some 15-20 years later (14, 15). In patients with unilateral cryptorchidism, this correlation is not so universal (15). A study of delayed results of orchiopexies done before the age of two has shown that the presence of Ad spermatogonia in biopsies is crucial for future fertility (6). It has been considered that early orchiopexy in patients with a normal number of germ cells guarantees good fertility. It is not that simple. Up to 36% of patients with cryptorchidism and a normal number of germ cells at the time of biopsy had an abnormal spermiogram later in adulthood. Those patients did not have an adequate "priming" effect after birth, which would induce timely development of gonocytes and their transformation into Ad spermatogonia. On the other hand, patients who had an adequate "priming" effect and who developed Ad spermatogonia in the first year of life had normal fertility in adulthood.

In order to preserve the fertility of patients with cryptorchidism who underwent orchiopexy during the first two years of life, but whose biopsy showed a lack of Ad spermatogonia, Hadziselimovic and Herzog treated those patients with a low dose of busereline over the period of 6 months (17). Post-therapeutically, there was a statistically significant increase in the number of spermatogonia (including Ad spermatogonia) *per* tubule. These patients were followed into adulthood and those having received hormonal therapy had better spermiograms compared to those who underwent orchiopexy alone.

In our study, the mean age of patients operated on for undescended testis was 5.62±3.78 years, which is well above the optimal age for surgical therapy of cryptorchidism. Most of the patients were operated on shortly after the first consultation with a pediatric surgeon, so the delay originated from primary health care.

We found that out of 165 testicular biopsies, Sertoli cells only were present in 61 (37.0%), 78 testes had spermatogonia but without Ad spermatogonia, while only 26 (15.7%) testes had normal histology (with both Ap and Ad spermatogonia). This is a very low percentage of normal biopsies, since it has been shown that other regions have a much higher percentage of normal biopsies (Philadelphia 40.7% and Switzerland 38.2%) (18). We still do not have an explanation for these finding, but we hope that we will be able to explain it with further investigations.

CONCLUSION

Despite continuous education of pediatricians and pediatric surgeons, the mean patient age (5.62 years) at the time of treatment is still by far above the desired age (up to two years). It is commendable that an increasing number of patients undergo biopsy during orchiopexy, but it is discouraging that 84.3% of patients had poor histology at the time of surgery. We hope that postoperative hormonal therapy will be able to provide these patients with normal fertility in adulthood.

Authors declare no conflict of interest.
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S a ž e t a k

KRIPTORHIZAM – NAŠI REZULTATI I PROTOKOL LIJEČENJA

J. Varga, D. Živković, D. Vuković, Đ. Gajdobranski, D. Šarac

U ovoj studiji analizirali smo bolesnike operirane zbog kriptorhizma na Klinici za pedijatrijsku kirurgiju tijekom dvogodišnjeg razdoblja (2008.-2009.). Analiza je obuhvatila dob bolesnika, stranu zahvaćenu kriptorhizmom, položaj testisa, operacijski pristup (otvoreni, laparoskopski), tip operacijskog zahvata (orhiopeksija, orhiektomija s ugradnjom testikularne proteze) i rezultate histopatološke analize testisa podvrgnutih biopsiji. Tijekom ispitivanog razdoblja operirana su zbog kriptorhizma 192 bolesnika srednje dobi 5,62±3,78 godina. Jednostrani kriptorhizam utvrđen je kod 161 (83,9%) bolesnika, u 93 (57,8%) od njih desnostrani. Ukupno su operirana 223 testisa, 22 (9,9%) od njih u predskrotalnom položaju, 174 (78%) u ingvinalnom položaju i 27 (12,1%) u intraabdominalnom položaju. Laparoskopska pretraga provedena je u 37, orhiopeksija u 27 i resekcija ostatnog testisa s istodobnom ugradnjom testikularne proteze u preostalih 10 bolesnika. Intraoperacijska biopsija izvedena je na 165 (74%) testisa. Usprkos stalnoj izobrazbi srednja dob bolesnika od 5,62 godine u vrijeme liječenja prelazi poželjnu dob od dvije godine. Preporuča se izvođenje biopsije za vrijeme orhiopeksije kod sve većeg broja bolesnika.

Deskriptori: KRIPTORHIZAM – kirurško liječenje; PROTOKOL LIJEČENJA; BIOPSIJA; DIJETE; DIJETE, PREDŠKOLSKO

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