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ANDROLOGY

Original Article

Clinical and histopathological results of the adult patients with unilateral cryptorchidism patients

Erişkinde tek taraflı inmemiş testis serimizin klinik ve histopatolojik sonuçları

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ABSTRACT

Objective: To evaluate the clinical and histopathological results of adult unilateral cryptorchidism patients.

Material and methods: Data from adult unilateral cryptorchidism patients that underwent orchiectomy in our clinic between between January 2004 and March 2013 were retrospectively evaluated. Patients were divided into three groups as intra-abdominal, inguinal canal and superficial inguinal region according to the location of the undescended testes. Patients were also grouped according to their testicular volume (<4 cc, 4.1-12 cc, and >12 cc). Histopathology results of orchiectomy specimens were classified as follows: 1. Sertoli cells only, testicular atrophy and vanished testis (anorchia) 2. Hypospermatogenesis, and 3. Maturation arrest. Patients were grouped as normospermia, azoospermia and oligo/astheno/teratospermia groups according to semen analysis results. Correlations between testicular localization, testicular size, semen analysis and pathology results were evaluated. Incidental tumor detection rates were also calculated.

Results: Two hundred and forty-four adult unilateral cryptorchidism patients underwent orchiectomy in our clinic. There was no significant relationship between location of the testis and testicular pathology results (p=0.707). Most common semen analysis results was normospermia in patients with high testicular volume group however azoospermia and oligoasthenospermia observed commonly in patients with low testicular volume group. There was a significant relationship between testicular volume and semen analysis results (p=0.023). No significant relationship was observed between semen analysis and pathological results (p=0.929). After an evaluation of all factors with possible effects on the semen analysis results, only testicular volume (p=0.036) was found to have a significant impact. Only one case (0.4%) was incidentally diagnosed seminoma after a review of 233 patients with available histopathological results on record.

Conclusion: Adult unilateral cryptorchidism has a minimal effect on male fertility or even this effect can be overlooked. Low detection rates of incidental germ cell tumors also make an orchiectomy decision questionable in such cases.

Keywords: Adult; orchiectomy; pathology; undescended testis.

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ÖZ

Amaç: Erişkin tek taraflı inmemiş testisi olan hastaların klinik ve histopatolojik verilerinin değerlendirilmesi.

Gereç ve yöntemler: Kliniğimizde Ocak 2004 - Mart 2013 tarihleri arasında tek taraflı inmemiş testis tanısıyla orşiektomi uygulanmış olan erişkin hastalar retrospektif olarak incelendi. Hastalar inmemiş testisin lokasyonuna göre intraabdominal, ingüinal kanal içi ve yüzeyel ingüinal bölge olmak üzere gruplara ayrıldı. Testis hacimlerine göre de gruplandırıldı (<4 cc, 4,1-12 cc, >12 cc). Orşiektomiden sonra histopatolojik sonuçlar gruplandırılarak tanımlandı 1) Sertoli cell -only, testiküler atrofi ve kayıp testis (anorşi) 2) Hipospermatogenez, 3) Matürasyon arresti. Semen analiz sonuçlarına göre de normospermi, azoospermi ve oligo/asteno/teratospermi gruplarına ayrıldı. Testislerin lokasyonu, testis hacmi ve semen analiz sonuçları ile patolojik sonuçların korelasyonu incelendi. Ayrıca insidental tümör saptanma oranı da hesaplandı.

Bulgular: Kliniğimizde 244 erişkin tek taraflı inmemiş testise orşiektomi uygulandı. Testis lokasyonu ile testis patoloji sonuçları arasında anlamlı ilişki saptanmadı (p=0,707). Yüksek hacimli testislerde normospermi, düşük hacimlilerde ise azoospermi ve oligoastenospermi daha fazla görüldü. Testis hacmi ile semen analiz sonuçları arasında anlamlı ilişki belirlendi (p=0,023). Semen analizi ile patoloji sonuçları arasında anlamlı ilişki saptanmadı (p=0,929). Semen analiz sonuçlarını etkilemesi muhtemel tüm faktörler incelendiğinde, sadece testis hacminin anlamlı etkisi olduğu görüldü (p=0,036). Histopatolojik sonucu bilinen 233 olgudan yalnızca 1'inde (%0,4) insidental seminom saptandı.

Sonuç: Erişkin tek taraflı inmemiş testisin erkek fertilitesi üzerindeki etkisi minimaldir hatta gözardı edilebilir gibi görünmektedir. İnsidental olarak germ hücreli tümör saptanma oranının çok düşük olması, bu olgularda orşiektomi yapmanın gerekliliğini sorgulanabilir hale getirmektedir.

Anahtar kelimeler: Erişkin; orşiektomi; patoloji; inmemiş testis.

Introduction

Cryptorchidism is the most common congenital genital disorder seen in male infants. It is diagnosed in 2-4% of full-term and 20-30% of pre-term infants.[1,2] Probability of spontaneous self-descent in scrotum is low if the testicles do not descend within the first six months after birth. Spermatogenesis decreases over time in undescended testicles. Germ cells begin to decrease irreversibly after the age of two. Therefore, surgery which is the standard treatment, should be done as soon as possible after 6th month of life.

Only 1% of the infants with cryptorchidism reach the adulthood without any treatment.[3] A common view among clinicians is that undescended testicles in adults do not contribute to fertility.[4] Although Leydig cells are resistant to damage, their endocrine functions decrease with time.[5] Moreover, carcinoma in situ is seen in undescended testicles with the ratio of 1.7% which is higher than the normal population and 10% of testicular tumors are thought to arise from undescended testicles.[6]

In reference to this, orchiectomy is offered to adult patients with undescended testicles as an option in addition to close monitoring and follow-up.[7] In our study, the clinical and histopathological results in a large series of adult patients with unilateral undescended testicle were evaluated.

Material and methods

Regular follow-up or orchiectomy treatment options were offered to adult patients with unilateral undescended testicles who came to our clinic. Data from adult patients with unilateral cryptorchidism patients that underwent orchiectomy in our clinic between January 2004 and March 2013 was retrospectively evaluated.

Before surgery, physical examination, inguinal/pelvic ultrasonography, semen analysis and tests for testicular tumor markers [alpha fetoprotein (AFP), beta human chorionic gonadotropin (β-HCG) and lactate dehydrogenase (LDH)] were performed in all patients. According to ultrasonography results, patients were divided into intra-abdominal, inguinal canal and superficial inguinal region groups. Testicular volume was calculated based on pathological specimen measurements. Patients were also grouped according to their testicular volume: (<4 cc, 4.1-12 cc, and >12 cc).

All cases had adequate archival tissue for analysis in the pathology department of the same medical center. Hematoxylin and eosin (H&E) stained slides of formalin-fixed paraffin-embedded tissues were evaluated by a single pathologist (IY) using light microscopy without any prior knowledge about the clinical features of cases. Each orchiectomy specimen consisted at least 3 random sections of the testicles. Histopathology of orchiectomy specimens was examined in three groups. First group consisted of cases with Sertoli cell- only syndrome (SCO), testicular atrophy and anorchia. Second group was classified as hypospermatogenesis and third group as maturation arrest. Representative H&E sections of cases with hypospermatogenesis (a), maturation arrest (b) and Sertoli cell- only syndrome (c) are shown in Figure 1.

Testicular sizes were retrieved from the pathology reports.

Patients were categorized in groups of normospermia, oligo/astheno/teratospermia and azoospermia according to the results of their semen analysis.

The study has been conducted in accordance with the ethical principles of Declaration of Helsinki.

Statistical analysis

Data for the study were collected, tabulated, and statistically analyzed and compared using Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) software version 16.0 The

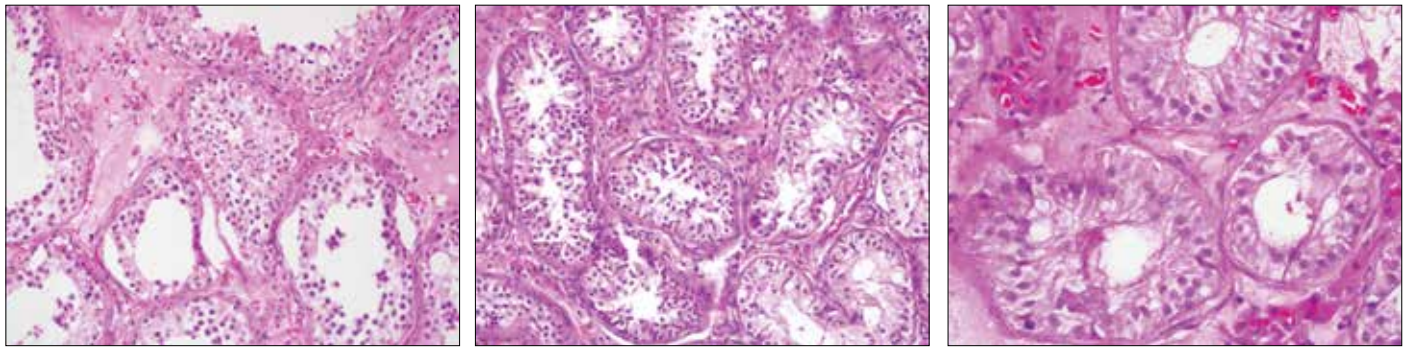

Figure 1. a-c. Representative H&E sections of cases with hypospermatogenesis (a), maturation arrest (b) and Sertoli cell- only (c). a) An example of hypospermatogenesis; all cell types (Sertoli cells, spermatogonia, spermatocytes and few spermatids) with a low level of cellularity can be seen within the seminiferous tubules (x200). b) In this section of maturation arrest, there are numerous spermatogonia, few spermatocytes and no spermatid (x200). c) An example of Sertoli cell- only, with a total absence of germ cells. Prominent nucleoli of Sertoli cells, mild thickening of the peritubular layer and increased number of Leydig cells in the interstitial area can be seen (x400)

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Table 1. Histopathology results according to location of testes in patients with unilateral undescended testis

		Histopathology results				
		Hypospermatogenesis n (%)	Maturation arrest, n (%)	SCO, atrophy, vanishing testicle, n (%)	Total, n (%)	p
Testicular location	Intraabdominal	0	7 (15.9)	20 (11.5)	27 (12.1)	
	Inguinal canal	3 (75)	32 (72.7)	137 (78.7)	172 (77.5)	0.187
	Superficial inguinal pouch	1 (25)	5 (11.4)	17 (9.8)	23 (10.4)	
Total		4	44	174	222	

SCO: Sertoli cell- only syndrome

data was expressed by way of mean±standard deviation, number or percentage according to its type. Correlation between testicular localization, testicular size and semen analysis and histopathological examination results were also evaluated. *Chi*-square test, Pearson's correlation analysis and linear regression analysis were used in the statistical comparison of the groups, and p-values were estimated and considered statistically significant if <0.05. In addition, incidental tumor detection rates were determined.

Results

Data from 244 adult patients who were orchiectomized for unilateral cryptorchidism were retrospectively analyzed. Pathological results of 233, testicular volume of 222 and semen analysis results of 97 patients were obtained from patient records. Data of 222 cases with known testicular volume, location and pathology results were evaluated separately from 97 cases with known semen analysis. Mean age of patients was 21.26±0.85 and median age was 21 (19-24). Mean testicular volume of pathological specimens was 6.90±5.81 cc [median 6 cc (0.1-30)]. One hundred and fifty-five patients were diagnosed with Sertoli cell-only (SCO) syndrome, 45 with maturation arrest, 5 with hypospermatogenesis, 17 with testicular atrophy, 1 with seminoma and 10 with vanished testicle (anorchia). When those histopathological results are grouped, 182 cases had SCO/testicular atrophy/vanished testicle (anorchia), 45 had maturation arrest and 5 were diagnosed with hypospermatogenesis. In terms of testicular location, 27 undescended testes were localized in the intraabdominal cavity, 173 cases in inguinal canal and 23 cases in superficial inguinal pouch. Evaluations of testicular volume indicated testicular volumes below 4 cc (n=63), 4.1-12 cc (n=137), and > 12 cc (n=22) in respective number of patients. After a thorough review of semen analysis results, normospermia (n=59), azoospermia (n=5) and oligo-/astheno-/teratospermia (n=33) were detected out of 97 patients. Chi-square test did not demonstrate significant correlations between these parameters (p=0.707) (Table 1).

In each location, the most common pathology was "Sertoli cell-only (SCO) syndrome". Vanishing testicle (anorchia) was not remarkable in distal regions. No significant relation was found between histopathology results and testicular locations in <4 cc, (Table 3) 4.1-12 cc (Table 4) and >12 cc (Table 5). Most common pathologies were SCO syndrome and maturation arrest in all groups and most common location was inguinal canal.

Out of the 233 patients with available histopathology results, incidental seminoma was found only in one case (0.4%) and that was in 4-12 cc groups. Testicular mass was not observed in this patient's USG. Histopathological examination of this patient also revealed diffuse intratubular germ cell neoplasia. The greatest dimension of seminoma was measured as 1.2 mm. Atypical cells showed immune-reactivity for Placental-like Alkaline Phosphatase (PLAP) with cytoplasmic membrane staining in addition to PAS positivity. Normospermia was mostly seen in cases with high-testicular volume and azoospermia/oligo-/asthenospermia which was common in low-testicular volume group. There was a significant correlation between testicular volume and results of semen analysis (p=0.023) (Table 6). However, any significant correlation was not found between semen analysis and histopathology results (p=0.929).

When all groups were evaluated in combination to determine which factor or factors effect the results of semen analysis using a linear regression analysis model, testicular volume was the only factor that effected the results of semen analysis (p=0.036). Neither histopathology results (p=0.292) nor testicular location (p=0.293) had a significant effect.

Discussion

It is a widely accepted fact that the contribution of undescended testicles to male fertility in adults is little or none.[3,4,8] When patients who underwent orchiopexy or orchiectomy during childhood were compared with untreated patients with unilateral cryptorchidism.[4,9] no significant difference was found in terms of parameters of semen analysis, testicular volume and gonadotropin levels. Normospermatogenesis was seen in only one patient out of 52 adult cryptorchidism cases. SCO was seen in 30 (58%), maturation arrest in 15 (28.5%) and testicular agenesis

Table 2. Histopathology results according to testicular volume groups in patients with unilateral undescended testis

		Histopathology results				
		Hypospermatogenesis	Maturation arrest	SCO, atrophy, vanishing testicle	Total	p
Testicular volume groups	0.1-4 cc	0	12 (28.6)	51 (29.1)	63 (28.5)	
	4.1-12 cc	3 (75)	24 (57.1)	109 (62.3)	136 (61.5)	0.109
	≥12.1 cc	1 (25)	6 (14.3)	15 (8.6)	22 (10)	
Total		4 (1.8)	42 (19)	175 (79.2)	221	

SCO: Sertoli cell-only syndrome

Table 3. Histopathology results according to location in testicular volume group of 0.1-4 cc in patients with unilateral undescended testis

		Histopathology results			
		Maturation arrest	SCO, atrophy, vanishing testicle	Total	p
Location	Intraabdominal	4 (28.6)	10 (71.4)	14 (22.2)	
	Inguinal canal	8 (17.4)	38 (82.6)	46 (73)	0.447
	Superficial inguinal pouch	0 (0)	3 (100)	3 (4.8)	
Total		12 (19)	51 (81)	63	

SCO: Sertoli cell-only syndrome

Table 4. Histopathology results according to location in testicular volume group of 4.1-12 cc in patients with unilateral undescended testis

		Histopathology results				
		Hypospermatogenesis	Maturation arrest	SCO, atrophy, vanishing testicle	Total	p
Testicularlocation	Intraabdominal	0	2 (20)	8 (80)	10 (7.5)	
	Inguinal canal	2 (1.8)	18 (16.7)	88 (81.5)	108 (81.2)	0.134
	Superficial inguinal pouch	1 (6.7)	3 (20)	11 (73.3)	15 (11.3)	
Total		3	23	107	133	

SCO: Sertoli cell-only syndrome

in 6 (1.5%) cases. Therefore, the authors argued that undescended testicles do not have an effect on fertility.[8] In addition, the authors reported azoospermia and oligospermia in 83% of the cases after an assessment of biopsy samples taken during orchiopexy performed after puberty.[8]

In a patient series consisting of 100 adults with 43 palpable and 57 non-palpable testes, normal spermatogenesis was not seen in any of the patients with intra-abdominal or atrophic testicle. However, 5% of the intracanal testicles had normal spermatogenesis. In addition, 76% of those cases had hypospermatogenesis and 19% were diagnosed with SCO syndrome.[3] In our study, we diagnosed 5 cases with hypospermatogenesis, 45 with maturation arrest and 182 with SCO syndrome/atrophy/vanishing testicle (anorchia). When testicular localization and size were separately evaluated, each of them did not show a predictive value in determining testicular histopathology. Moreover, the relationship between results of histopathology and semen analysis was insignificant (p=0.929). These findings support the hypothesis that undescended testicle in adult patients has little or no effect on the results of semen analysis. In another study that assessed post-orchiopexy sperm count results of adult patients with undescended testicle, orchiopexy decision was questioned since there was no positive change in testicular sperm extraction (TESE) performed following orchiopexy.[10] One of the main functions of testicles is to produce androgens. Even though Leydig's cells are more resistant to damage, endocrine functions tend to decrease in adult patients with cryptorchidism.[5] In a study about the effects of orchiectomy on serum testosterone levels in adult patients with

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Table 5. Histopathology results according to location in testicular volume group of >12 cc in patients with unilateral undescended testis

		Histopathology results				
		Hypospermatogenesis	Maturation arrest	SCO, atrophy, vanishing testicle	Total	p
Location	Intraabdominal	0	0	1	1	
	Inguinal canal	1 (6.7)	4 (26.7)	10 (66.6)	15	0.889
	Superficial inguinal pouch	0	2 (40)	3 (60)	5	
Total		1	6	14	21	

SCO: Sertoli cell-only syndrome

Table 6. Semen analysis results according to testicular volume in patients with unilateral undescended testis

Testicular volume	Normospermia, n (%)	Oligoasthenospermia, n (%)	Azoospermia, n (%)	n	p
0-4 cc	8 (36.4)	13 (59.1)	1 (4.5)	22	0.023
4.1-12 cc	37 (66.1)	16 (28.6)	3 (5.4)	56	
>12 cc	9 (75)	3 (25)	0	12	
Total	54 (67.5)	32 (27.5)	4 (5)	90	

cryptorchidism, any change in serum testosterone levels was not reported after orchiectomy in those cases.[11]

About 10% of testicular tumors presumably arise from undescended testicles.[12] A germ-cell tumor was diagnosed 16 months after detection of carcinoma in situ (CIS) in a case with undescended testicle.[6] In a study where 300 adult patients with cryptorchidism were evaluated, 5 patients (1.7%) had CIS. Therefore, since it is clear that incidence of CIS is higher in adult patients with cryptorchidism relative normal population, biopsy is indicated in these patients. The United Kingdom Testicular Cancer Study Group reported that undescended testicles are associated with testicular cancer formation.[13] Tumor risks can be eliminated if orchiopexy is performed within the first 10 years of life.[14] Cancer risk increases in older patients. It was reported in a previous study that malignancy risk increases in testicles with a more proximal location. In addition, another study reported that atrophic testicles carry a higher risk for tumors. For this reason, orchiectomy is indicated in adult patients with cryptorchidism.[15-19] Although recently remarkable developments in the treatment of germ-cell neoplasia have been achieved, together with a decrease in disease-specific and perioperative mortality rates, orchiectomy can be performed in men up to 50 years of age with unilateral cryptorchidism.[20] In the literature, there are several studies about incidence of incidental tumor in adult patients with cryptorchidism who had undergone prophylactic orchiopexy for tumors. In a study performed on 100 patients, neither tumors nor CIS was diagnosed in any of the patients[3] whereas Kocak et al.[21] investigated the frequency of CIS among 42 adult men (20 to 27 years of age), who presented with undescended testes, and CIS was detected in only one patient (2.3%). Rogers et al.[4] detected CIS in only 2 (4%) out of 50 cases, and in another recent study one case of CIS out of 51 patients was found.[22] However it must be kept in mind that about 50% of CIS cases can develop into invasive tumors within 5 years.[6,23,24] In our study, we diagnosed only one patient with seminoma (0.4%) by coincidence On the contrary, a study done in Welvaart-Netherlands concluded that orchiectomy should be performed only after an accurate tumor diagnosis is made since the exact risk of cancerogenesis is unknown.[25]

The most important limitation of our study is its retrospective design. Furthermore, post-operative semen analyses as well as preoperative and postoperative hormonal evaluations were not made. Undescended testicles do not only affect spermatogenesis, but also can change endocrine profile. Since patients with undescended testicles are under risk of decreased testosterone production during their lifetime, orchiectomy of the undescended testicle is definitely going to reduce Leydig cell count and therefore, endocrine capacity of gonads. Orchiectomy of a hormonally active testicle may increase the risk for hypogonadism in young patient population. However, SCO, atrophy, and vanishing testicle were found in 78.4% of the patients in our study. It is not possible to talk about the hormonal activity of these testicles, and there is no possibility of development of postoperative hypogonadism in these patients. While there has been no post-operative hormonal evaluation, it should not be considered as a limitation of the study.

In conclusion, the effect of unilateral cryptorchidism of adults on male fertility seems to be of minimal degree or even non-existent.

Low rates of diagnosis of incidental germ cell tumors also make the decision of orchiectomy questionable in such cases. This study is characterized as one of the largest series in the literature on this subject. Detailed explanations and evaluations of testicular histopathology and semen analysis results based on testicular volume and location provided an additional contribution to the literature.

Ethics Committee Approval: Because of the retrospective nature of the study, ethics committee approval was not required. It has been written in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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