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Original Article

Histopathological study of the fertility components of undescended testes in boys of different age group

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Abstract

Background: Undescended testes presents the most common male developmental abnormalities, with infertility frequently observed in unilateral as well as bilateral forms. In that study, we evaluated the histological parameters of Undescended testes based on patient's age and we recommended for the optimal timing for orchiopexy.

Objective: To evaluate the histological parameters of undescended testis and determine the optimal timing for orchiopexy.

Methods and Materials: This cross-sectional study included 30 patients with undescended testis(es) in the department of paediatric surgery, BSMMU. After taking relevant history, examination findings and investigation reports of all the study subjects were recorded in the pretested data collection sheet. Then biopsy specimens were collected from the selected testes during orchiopexy and analyzed the parameters including mean tubular diameter (MTD), mean tubular fertility index (MTFI) germ cell count (GCC), Sertoli cell index (SCI) and interstitial fibrosis index (IFI)

Results: The MTFI and GCC in children <1 years of age were significantly higher than those of other older age group. (P= 0.011 & P= 0.003) The MTFI, GCC and IFI were significantly better in patients <2 years of age when compared to those of > 2years. IFI in the > 5-years group was significantly higher than those of any of the other younger age groups (P < 0.05). Other parameters such as testicular volume, MTD and SCI showed no statistically significant difference between the age groups studied.

Conclusions: This study revealed that higher number of germ cells exists in the tubules between 6 months and 1 year. After first year of life, the major germ cell parameters deteriorate continuously, thus we recommended that orchipexy should be performed, between 6 months and 1 year but no later than 2 years for preserving future fertility.

Keywords: age,undescended testis, histopathology, surgery, treatment.

Introduction

Undescended testis is one of the most common malformations of testis in the male population. Approximately one percent of the male population has one or both testes undescended. Sterility and malignancy are the two main problems resulting from the undescended state of the gonad[1]. Undescended testis (UDT) denotes a clinical condition in which one or both of the testes fail to reach the corresponding scrotal sac after birth in an otherwise normal appearing male child[2].Temperature wthin the scrotum is about 3 degree lower than abdominal cavity and 1-2 degree lower than inguinal canal. This lower temperature is essential for proper development and maturation of both germ and non –germ cells within the testicular parenchyma.This is supported by the fact that infertility is 3.5 times more frequent in patient with bilateral cryptorchidism and those with unilateral ones and 6 times more frequent than normal population[3].

Testicular biopsy analysis is currently the most effective method for identifying boys at risk of infertility after successful surgery for cryptorchidism, because a positive correlation exists between testicular histopathology at orchiopexy and future fertility in patient with cryptorchidism[4].

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Orchiopexy remains gold standard for management of the crypptorchid testis. One of the goals of orchiopexy is to prevent further testicular degeneration that can impair fertility or other endocrine functions. Less than 30% of referring paediatricians and family practioners believe that the timing of the procedure should be between 6-12 months of age[5].

Impairment of maturation and subsequent loss of germ cells are well-recognized causes of infertility associated cryptorchidism[6]. Inspite of many histological data which suggest the importance of early orchiopexy, there is limited histological evidence that supports the importance of orchiopexy as early as within the first year of life to maintain fertility potential. In this study, we evaluate the histological findings of the undescended testes based on patient's age to obtain data to determine the optimal timing for orchiopexy.

Patients

During the period October 2016 - September 2018,We studied 30 patients of undescended testis , aged between 6 months and 18 years in tertiary hospital ,Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka ,Bangladesh. Preoperatively, we had to explain the risks and benefits of testicular biopsies. Informed written consents were obtained from all of the parents whose children participated. All of the patient with disorder of sexual differentiation, Prader-willi syndrome, Pierre-Robin syndrome or other systemic disease were excluded.

Methods

All the fit patients were underwent testicular exploration with an aim to correct their anatomical positions of testes. Biopsy specimen was taken from each of the undescended testes during orchiopexy. Testicular tissues were fixed in Bouin's solution and embedded in paraffin wax.Very fine absorbable synthetic sature materials were used to repair the testicular wounds.In order to investigate the fertility potential in the enrolled patients, we analyzed the histological findings using the following five parameters. We selected tubules which were as close to cross-sectioned as possible.

Mean tubular diameter (MTD): We selected 20 tubules with a round circular shape and measured the tubular diameter for each using a micrometer eyepiece (Olympus, Tokyo, Japan), and calculated the mean tubular diameter.

Mean tubular fertility index (MTFI): We calculated the percentage of the tubules containing at least one germ cell among 50 randomly selected tubules under a high power field (x 400).

Germ cell count (GCC): We calculated the mean number of germ cells per tubule in a total of 50 randomly selected tubules.

Sertoli cell index (SCI): We measured the mean number of sertoli cells per somniferous tubule among the 50 randomly selected tubules under a high power field.

Interstitial fibrosis index (IFI). We defined the degree of peritubular tissue fibrosis by a four group grading system: (0) 0%; (1) 1-25%; (2) 26-50%; and (3) 51% or more.

Ethical Considerations

In accordance, The Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU) was approved all aspect of this study. In particular, approval was given for research involving the use of material (data, documents, records, specimens) that had been collected for this study.

Statistical analysis

Statistical evaluation was performed using SPSS version 24 for data sorting and analysis. Analysis included comparison of individual group means. Statistical analysis was performed using Student's unpaired 't' test; 'r' test was used for comparison and correlation. P value of <0.05 was considered as statistically significant.

Results

Age range of the patients in the study was 6 months to 15 years. The mean age 7.8 years. Patients belonged to the age group <1 yr, were 2 (6.7%); number of patients in age group 1-2 yrs, 3-4 yrs, 5-6 yrs, 7-8 yrs, and >8 yrs, were 7 (23.3%), 2(6.7%), 4(13.3%), 5(16.7%), 10(33.3%) respectively.

In this study, morphology of undescended testes on exploration, 17 (56.7%) were apparently normal size for age and 13 (43.3%) smaller for the age.

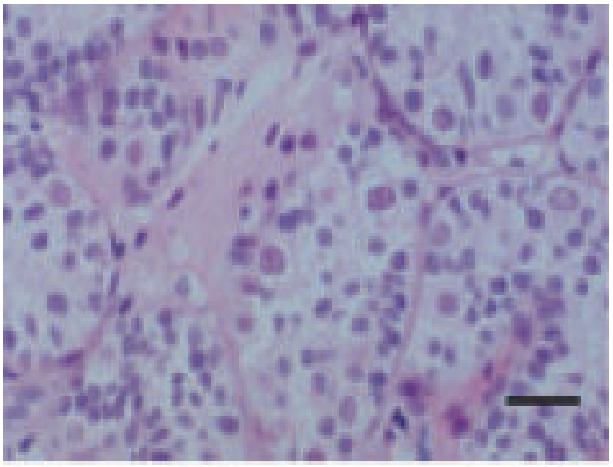

Fig.-1 *(9 months old boy)*

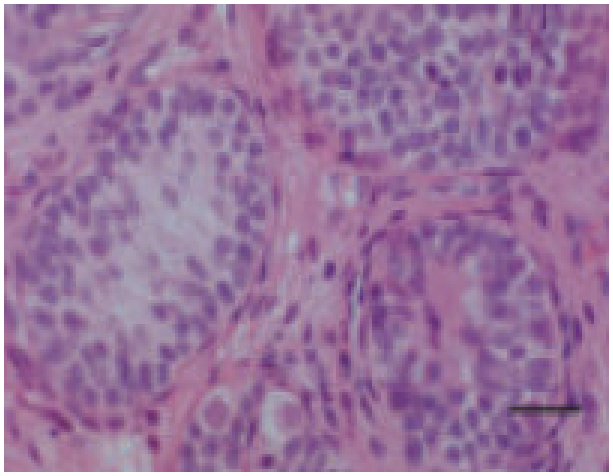

Fig.-2 *(1 year and 6 months old boy)*

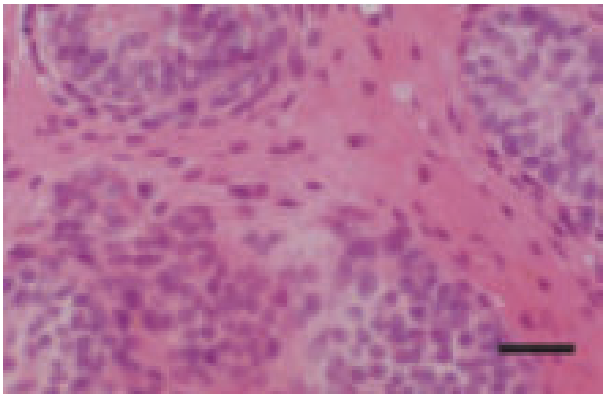

Fig.-3 *(5 years old boy)*

Fig. 1-3 Histological features demonstrate that the number of germ cells were reduced and interstitial or peritubular fibrosis were increased with increasing patient age in undescended testes.

The first finding from our results was that children with cryptorchidism presented very late to the paediatric surgery departments in our region; 63% were older than 5 years (Table- I). Morphology of undescended testes on exploration reveled, 17 (56.7%) apparently normal size for age and 13 (43.3%) smaller for the age (Table II).

Table I: *Distribution of the study subjects according to age (n=30)*

Age (years)	Frequency (n)	Percentage (%)
<1	2	6.7
1 - 2	7	23.3
3 - 4	2	6.7
5 - 6	4	13.3
7 - 8	5	16.7
>8	10	33.3
Total	30	100.0

Table II: *Morphology of the undescended testis on exploration of the study subjects (n=30)*

Site involvement	Frequency (n)	Percentage (%)
Apparently normal size for age	17	56.7
Smaller for age	13	43.3
Total	30	100.0

In patients of undescended testes demonstrated that the histological parameter of fertility components such as MTFI and the GCC in <1 year were significantly higher than those of any other age group including patients 1-2 years of age. (Table III) In addition, we observed that IFI was progressive and was most remarkable for the >5-years group.

Table IV shows relation between age and MTD, MTFI, SCI, GCC and IFI; among the five parameters only two parameters (MTFI and GCC) were negatively correlates with age.

Table-III: *Histological parameters of the cryptorchid testes according to the different patient age group*

Age (years)	MTD (µm)	MTFI (%)	SCI (per tubule)	GCC (per tubule)	IFI
<1	8.50 ± 2.12	30.00 ± 0.00	19.50 ± 2.12	5.00 ± 1.41	1.00 ± 0.00
1 - 2	6.71 ± 1.80	18.57 ± 11.07	29.43 ± 4.04	5.00 ± 3.06	0.86 ± 0.69
3 - 4	6.50 ± 0.71	31.00 ± 26.87	33.50 ± 16.26	2.63 ± 3.36	1.00 ± 0.00
5 - 6	7.25 ± 0.96	11.50 ± 12.79	33.00 ± 6.68	1.53 ± 0.95	2.00 ± 0.82
7 - 8	5.14 ± 2.52	6.60 ± 5.13	22.60 ± 2.88	1.40 ± 0.55	1.40 ± 0.55
>8	8.00 ± 3.20	10.11 ± 9.52	33.44 ± 10.71	1.80 ± 1.76	1.33 ± 0.50
p-value	0.398^{ns}	0.043*	0.104^{ns}	0.024*	0.098^{ns}

ANOVA test was done to measure the level of significance
*=Significant
ns= non significant

Table IV: *Correlation of age with MTD, MTFI, SCI, GCC and IFI*

Age (year)	Parameters	r value	p-value
<1	MTD (µm)	+0.155	0.422^{ns}
1-2	MTFI (%)	-0.463	0.011*
3-4	SCI (per tubule)	+0.234	0.221^{ns}
5-6	GCC (per tubule)	-0.531	0.003*
>7	IFI	+0.319	0.092^{ns}

Pearson's correlation was done to measure the level of significance
Relationship between age and MTFI and GCC
*=Significant
ns= non significant

Discussion

Histological change associated with undescended testis is a matter of curiosity. Although most investigators had agreed about smaller size in adult untreated UDT but in children always creates much controversy. The study of Konar et al.[7] revealed undescended testes are much smaller than normal in children.

The first finding from our results was that children with cryptorchidism presented very late to the paediatric surgery departments in our region; 63% were older than 5 years. It appears that although for the last two decades it has been stressed that cryptorchidism should be treated in early childhood, this concept has not much impact on paediatrician consultation. In addition, social and ethical prejudices of the parents still play an important role in the delayed referral of these patients to the surgeon.

In this study, morphology of undescended testes on exploration, 17 (56.7%) apparently normal size for age and 13 (43.3%) smaller for the age.

Nistal demonstrated that the MTFI levels at the time of biopsy show a direct correlation with the results of semen analysis in adult[8,9]. Cortes and Hadziselimovic showed that a GCC lower than 0.2 is associated with a higher risk of infertility in adulthood[10,11].

In this present study, histological features demonstrat that the number of germ cells was dramatically reduced and interstitial or peri tubular fibrosis was increased with increasing patient age in the undescended testes (Fig.1-3) .This observation of the study corresponds with the finding of Park et al.[12] who found similar result on their work with UDT.

Our data, from the cryptorchid testes, demonstrated that the histological parameter of fertility components such as MTFI and the GCC in cryptorchid patient <1

years were significantly higher than those of any other age group including patients 1-2 years of age (Table-III). In addition, we observed that IFI was progressive, and was most remarkable for the >5-years group. The major germ cell parametetrs, MTFI and GCC, as well as IFI were obviously better in the < 2-year group compared to those older than 2 years of age. After 2 years of age, the GCC fall, this corresponds with the finding of Park et al[12].

Our data shows that correlation of age with MTD, MTFI,SCI, GCC and IFI; among the five parameters only two parameters (MTFI and GCC) negatively correlates with age (Table- IV). This observation of the study corresponds with the finding of Lee et al.[13] who found similar result on their work on 53 children with UDT.

On the contrary, mean tubular diameter (MTD) and Sertoli cell index (SCI), which were not directly related to germ cells revealed no significant difference in the mean values for the age groups.

The risk for infertility is a well-known consequence of cryptorchidism. In the 1950s, orchiopexy was recommended in boys aged 10-15 years, in the 1970s in 5-6 years old boys. During the 1970s and early 1980s age of orchiopexy declined to 2 years of age. Currently orchiopexy is recommended between 6 and 12-18 months[14]. Most recently, the recommendation for intervention is as early as 6 month to 1 year. This recommendation is based on the clinical observation that spontaneous descent of the cryptorchid testis occurs by 3 months of age in most boys[15].

The first step of germ cell maturation after birth is transformation of the gonocyte into adult dark spermatogonia (Ad), which is usually completed by 6 months of life. This critical step is known to be delayed and defective in patients with cryptorchidism. And thus the second transformation of the Ad spermatogonia into the primary spermatocyte, which normally begins at around age 3 years, also fails to occur in the cryptorchid testis[16].

Our histological findings suggest that the optimal age for orchiopexy should be between 6 months and 1 year, during which period delayed transformation but still a higher number of germ cells exist in the tubules. After the first year of life, the major germ cell parameters deteriorate continuously, and thus we also recommend that orchiopexy should be performed no later than 2 years in children with undescended testes for preserving future fertility.

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