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Cryptorchid testis histopathology in myelomeningocele patients

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Abstract *Purpose:* Cryptorchidism occurs in 25% of boys with myelomeningocele (MMC) compared to 3% of the general population. Testicular biopsy histopathology correlates with future sperm counts. We studied testicular histology in boys with cryptorchidism and MMC to investigate if the MMC influences histological findings.
Materials and methods: The study group consisted of six patients with MMC and undescended testis (UDT) who underwent orchiopexy and bilateral testis biopsy. Twelve testicular biopsies from six patients were compared to 40 biopsies from 20 UDT-only controls. Total germ cell count per tubule (TGC/T) and the percentage of adult dark spermatogonia (%Ad) in undescended and contralateral descended testes from the patients were compared with controls.
Results: In the study group, two had total absence of germ cells (TGC/T = 0) and three had severely reduced germ cells (TGC/T < 0.2). Four had total absence of Ad spermatogonia and the remaining two had severely reduced Ad spermatogonia (%Ad = 5). The mean TGC/T and %Ad in patients with UDT and MMC were conspicuously lower than controls. The differences did not reach statistical significance ($P = 0.09–0.29$).
Conclusion: These results suggest that patients with both MMC and UDT have a more severe reduction in total number and more severely delayed maturation of germ cells than do patients with UDT alone. With only six patients in this study, there was not the power to detect statistical significance. In addition to the reproductive problems due to erection and ejaculatory dysfunction in patients with MMC, this severe testicular histopathology may increase the risk of subfertility.

Introduction

Cryptorchidism has not been recognized as a significant urological problem in children with myelomeningocele (MMC) due to the fact that these boys have other more major neuro-urological issues. However, 25% of boys with

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myelomeningocele (MMC) as compared to 1–3% of the general population have cryptorchidism [1,2]. Fertility does remain an important issue for many of these boys.

Isolated cryptorchidism has been shown to be due to a forme fruste of hypogonadotropic hypogonadism [3,4]. The total germ cell count determined from testicular biopsies in boys with cryptorchidism correlates with future sperm counts [5–7]. We hypothesize that boys with MMC and cryptorchidism demonstrate more severe testicular histologic abnormality than that seen with isolated undescended testis (UDT), and thus are at potentially greater risk of future subfertility. We present an observational report comparing the testicular histopathology in boys with MMC and UDT to that of boys with isolated UDT.

Materials and methods

The study group consisted of six patients with MMC and UDT who underwent orchiopexy and bilateral testis biopsy between 1991 and 2000 (see Table 1). The level of MMC was thoracic in three boys and L2–3 in the remaining. All six patients had ventriculo-peritoneal shunts in place for hydrocephalus. Semi-thin sections of the bilateral testes biopsies obtained at orchiopexy were fixed in 2% gluteraldehyde in phosphate buffer, blocked in EMbed 812 (Electron Microscopy Sciences, PA, USA) and stained with toluidine blue. The 12 testicular biopsies (three scrotal, five upper scrotal or pubic tubercle, and four intra-abdominal) from the study group were compared to 20 age-matched and position-matched UDT-only controls (40 biopsies). Histomorphometric analysis, including total germ cell count per tubule (TGC/T) and percentage of all germ cells that were adult dark spermatogonia (% Ad), was performed on the undescended testis (UDT) and contralateral descended testis (CDT). At least 50 tubules were counted in each biopsy. Statistical analysis was performed using the exact Wilcoxon–Mann–Whitney test. The study was approved by the Institutional Review Board.

Results

The TGC/T and %Ad in patients with UDT and MMC were extremely low or absent (Table 1). Two had total absence of germ cells (TGC/T = 0), and three had severely reduced germ cells (TGC/T < 0.2). Four had total absence of Ad spermatogonia (%Ad = 0) and the remaining two had severely reduced Ad spermatogonia (%Ad = 5). The median TGC/T and %Ad in patients with UDT and MMC were lower than controls but the differences did not reach statistical significance (Table 2).

Table 1 Patients with MMC and UDT

Age	UUDT/BUDT	Position		TGC/T		%Ad	
		R	L	R	L	R	L
12 months	BUDT	T	T	0.11	0.14	0	0
12 months	UUDT	T	S	0.10	1.08	0	5
15 months	BUDT	A	A	0.51	0.24	0	4
14.5 years	BUDT	A	A	0	0	0	0
15 years	UUDT	S	T	0.13	0.13	0	0
16 years	UUDT	T	S	0	0	0	0

Normal values: TGC/T (12–15 months) = 1.5–2; TGC/T (14–16 years) = 15–16; %Ad (all ages) = 10%.
Total no. of testes: UDT = 9, CDT = 3.
Abbreviations: BUDT = bilateral UDT, UUDT = unilateral UDT, A = intra-abdominal, T = tubercle (outside external ring), S = scrotal, R = right testis, L = left testis.

Discussion

Boys with MMC have reproductive problems due to several abnormalities including ejaculatory and erectile dysfunction. Despite these problems, boys born with MMC have a good prognosis in terms of establishing long-term sexual relationships. In the series published by Laurence and Beresford, 16 of 28 were living with a steady partner and nine had fathered children [8]. While paternity is possible in patients with MMC, fertility is probably reduced.

Cryptorchidism poses additional risks due to poor spermiograms and subfertility [9–12]. The etiology of cryptorchidism has been suggested to be multi-factorial. Several factors postulated to be responsible for testicular descent include traction by gubernaculum, increase in intra-abdominal pressure, growth of the body wall and function of the genito-femoral nerve in gubernacular development [13–19]. A forme fruste of hypogonadotropic hypogonadism has been documented and may explain, in addition to the UDT, abnormal histology in both the undescended and contralateral descended testes [20–22]. Normally, at 2–3 months of age, a surge in serum levels of luteinizing hormone (LH) stimulates Leydig cells to produce a rise in testosterone that triggers the transformation of gonocytes, the fetal stem cells, into Ad spermatogonia, the adult stem cells for spermatogenesis [23,24]. At 5 years of age, a second lower surge of LH and testosterone stimulates Ad spermatogonia to transform into primary spermatocytes, the first step in meiosis. In boys with UDT, both of these androgen-mediated steps in germ cell maturation are delayed and defective [3,4]. The adult stem-cell pool of Ad spermatogonia either fails to develop at all or is severely reduced in size due to these failed steps in maturation. The presence of Ad spermatogonia may be the most important feature predicting future fertility (personal communication with F. Hadziselimovic, 2002). Impaired pituitary LH response to gonadotropin-releasing

Table 2 Statistical analysis (exact Wilcoxon–Mann–Whitney test)

Age	Median	TGC/T		%Ad	
		UDT	CDT	UDT	CDT
12–15 months	Patients ($n = 3$)	0.14	1.08	0	5.13
	Controls ($n = 22$)	0.57	0.46	0.71	7.69
	P value	0.09	NA	0.25	NA
14–16 years	Patients ($n = 3$)	0	0.06	0	0
	Controls ($n = 18$)	0.1	0.92	0	4.57
	P value	0.29	NA	1	NA

NA = not applicable.
Patients divided into pre-pubertal and post-pubertal age groups.

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hormone, impaired testis response to human chorionic gonadotropin and presence of hypergonadotropic hypogonadism (testicular failure) after puberty support this theory [25–28].

In boys with MMC, the presence of hydrocephalus might influence the hormonal environment by affecting the hypothalamic–pituitary axis [1]. Reilly and Oates examined testicular biopsies of 10 MMC impotent male adults with azoospermia [29]. They found Sertoli-cell-only tubules, supporting our findings of poor testicular histology in this population. Others contend that central nervous system abnormalities may contribute to the likelihood of cryptorchidism. In a study done by Hadziselimovic et al., of the 19 patients with omphalocele, all the boys with an associated brain malformation had cryptorchidism while those without a brain malformation had an incidence of cryptorchidism similar to the general population (1–3%), possibly suggesting an abnormality of the hypothalamic–pituitary axis [30]. All of our patients had ventriculo-peritoneal shunts placed as newborns. Availability of a comparison MMC population with UDT but without a central nervous system shunt might further elucidate any part that hydrocephalus plays in gonadal development.

Our study shows that patients with MMC usually have poorer testis histopathology than patients with isolated cryptorchidism. The small number of patients in this series falls short of the power required to detect statistical significance. Larger numbers, if available through perhaps a multi-center study, may confirm or refute our initial findings. This testicular histopathology adds to pre-existing fertility problems caused by erection and ejaculatory dysfunction. These boys require an aggressive and coordinated approach to maximize testicular function. It remains to be determined if the MMC patients with germ cell-depleted testes will benefit from gonadotropin therapy, which has been shown to be effective in improving the germ cell count and spermiograms in cryptorchid patients without associated MMC [31].

Conclusion

This study suggests that in patients with both MMC and UDT there is a more severe reduction in number and more severely delayed maturation of germ cells than in patients with UDT alone. This difference may be associated with the hydrocephalus associated with MMC. The severe testicular histopathology may increase the risk of subfertility in addition to the reproductive problems due to erection and ejaculatory dysfunction in these patients.

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