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Growth of Spontaneously Descended and Surgically Treated Testes During Early Childhood

Claude Kollin, Tina Granholm, Agneta Nordenskjöld and E. Martin Ritzén

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WHAT'S KNOWN ON THIS SUBJECT: There are no published prospective studies on the natural course and testicular growth in early childhood of spontaneously descended testes after birth compared with scrotal or surgically treated testes in boys with congenital cryptorchidism.

WHAT THIS STUDY ADDS: Data collected from this prospective study on the natural course and growth of the spontaneously descended testes add evidence-based data and recommendations on how to clinically manage boys with congenital cryptorchidism.

abstract

OBJECTIVE: To investigate whether in congenital unilateral cryptorchidism the growth of a spontaneously descended testis is normal, compared with the contralateral scrotal testis or similar to the growth of testes that failed to descend spontaneously and later underwent orchidopexy.

METHODS: Ninety-one boys with congenital unilateral cryptorchidism with later spontaneous descent of the initially retained testis were followed from birth (0–3 weeks) up to 5 years of age and compared with boys randomized to surgery at either 9 months ($n = 78$) or 3 years ($n = 85$) of age. Testicular volume was determined with ultrasonography.

RESULTS: Eighty-two percent of spontaneous descent occurred before 2 months of age. Twenty-two percent of these descended testes were later again found in a retained position. The spontaneously descended testis was smaller than its scrotal counterpart at all ages ($P < .001$). We also showed a significant difference in the testicular volume between the early and late treated boys from age 2 years and onward. At 2, 4, and 5 years of age, the volumes of the spontaneously descended testes were significantly larger than those of boys operated on at 3 years but similar to those operated on at 9 months.

CONCLUSIONS: We have shown that in boys with congenital unilateral cryptorchidism with later spontaneous descent, the originally retained testes show impaired growth compared with its scrotal counterpart from birth and onwards. Also, they are prone to later ascent to a retained position. Furthermore, the longer testes remain untreated the more they exhibit impaired growth. *Pediatrics* 2013;131:e1174–e1180

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KEY WORDS

undescended testis, cryptorchidism, treatment, spontaneous descent, testicular volume

Dr Kollin participated in conceptualizing and designing the study; coordinated the study; performed all surgical procedures; examined the patients prospectively, wrote, reviewed, and revised the initial manuscript; and approved the final manuscript as submitted. Dr Granholm participated in conceptualizing and designing the study and approved the final manuscript as submitted. Dr Nordenskjöld reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr Ritzén participated in conceptualizing and designing the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Incomplete descent of the testes is the most common anomaly in newborn boys. The prevalence in full-term newborns varies between 2% and 9%, decreasing to 1% to 3% at 3 months of age due to spontaneous descent.[1–4]

Interestingly, the accumulated prevalence of orchidopexies is 2% to 4%, indicating that some of the descended testes can ascend to a suprascrotal position after 1 year of age.[5,6] Other authors have agreed that acquired cryptorchidism is a reality and that in most cases (57%–78%) the condition will correct itself at puberty.[7–10] Alternatively, the high prevalence in prepubertal ages may be explained to some extent by misdiagnosing retractile testes as truly undescended.[11]

The John Radcliffe Hospital Cryptorchidism Study Group found that a considerable number of congenitally cryptorchid testes that descended between birth and 3 months of age were again cryptorchid at age 1 year.[6] Wohlfahrt-Veje et al defined this condition as *recurrent* cryptorchidism, to be distinguished from *acquired* cryptorchidism, where the testes were in a normal position at birth.[8] The cause of acquired or recurrent cryptorchidism is unclear.[12–14]

Histopathologic studies on these acquired forms of undescended testes show that they exhibit similar germ cell maldevelopment as in congenital cryptorchidism.[15,16]

The germ cell deterioration in undescended testes is at least partly due to relative hyperthermia. Elevated temperatures have been shown to have adverse effects on testicular function in animal models and in boys.[17–19] Also, supportive of this is that iatrogenic undescended testes (after hernia repair) exhibit a decreasing number of germ cells per tubular cross section as time in a suprascrotal position increases, indicating that these testes undergo a secondary damage.[20]

We previously investigated the testicular development from birth to 4 years of age, before and after orchidopexy at 9 months or 3 years of age. In unilateral cryptorchidism, most of the retained testes were significantly smaller than the scrotal counterpart already at birth. However, in a subgroup of these patients ($n = 22$), the undescended and scrotal testes were of the same size at birth. Over time, these retained testes showed significantly impaired growth compared with the scrotal ones, suggesting that testicular damage continued postnatally if the testes remained undescended. In summary, these results indicate that prenatal factors are important in the majority of cases but also that the suprascrotal position in itself is detrimental to testicular growth after birth.[21]

The retractile testis has been regarded as a variant of the normally descended testis and therefore would not require treatment. However, there are studies suggesting that retractile testes exhibit similar histologic changes as cryptorchid ones and therefore can be a cause of subfertility.[22–24] Retractility is attributed to the cremasteric reflex, which is most active between 5 and 6 years of age, but absent during the first months of life and during puberty.[25] Hack et al studied the prevalence of acquired cryptorchidism at different ages and concluded that the prevalence was 1.2% at 6 years, 2.2% at 9 years, and 1.2% at 13 years.[26] Thus, the high prevalence approximately coincides with a period when retractility is more common.

Similar to acquired cryptorchidism, a major part (77%) of the retractile testes will descend spontaneously into the scrotum by the age of 14.[27] This suggests that some cases of acquired cryptorchidism are in fact retractile testes and highlights the limitations of retrospective studies when it comes to the terminology and definition of truly undescended testes.

Thus, these 3 conditions (congenitally undescended, acquired, and retractile testes) show similar adverse histologic changes in the testes, suggesting subsequent risk of subfertility, possibly due to the suprascrotal position and secondary thermal effects.

Here we present a prospective study on the growth of testes that were undescended at birth but descended during the first few months and compare them with surgically treated testes at different ages. We hypothesize that a suprascrotal position of the testes from birth until spontaneous descent impairs testicular growth, compared with those that have been in the scrotum from birth and onward.

METHODS

Patients

This study is part of a larger study on the optimal age for orchidopexy. Boys with probable congenital cryptorchidism were recruited. The exclusion criteria were recognized syndromes, other birth defects or other pathologic conditions affecting the external genitalia, prematurity (<37 weeks of gestation) or previous groin surgery.

After confirmation of unilaterally undescended testis and after informed consent by the parents, the boys were included at ages 0 to 3 weeks. Some boys were not enrolled in the study until 6 months of age due to late referral. According to their neonatal records, these late referred were cryptorchid from birth. At age 6 months, all boys who were still cryptorchid were randomized to orchidopexy at either 9 months or 3 years of age as previously described.[21] In the present cohort of boys with unilaterally undescended testes, the normally descended contralateral scrotal testis was used as a reference.

For the current study, 254 boys in 4 subgroups were followed prospectively: group 1 consisted of those with unilateral cryptorchidism at birth but with postnatal spontaneous descent (n = 71), groups 2 and 3 were those with unilaterally undescended testes at 6 months who were randomized to orchidopexy at 9 months of age (group 2, n = 8) or 3 years of age (group 3, n = 85), and group 4 consisted of boys with ascending testes (n = 20). This last group was confirmed cryptorchid at birth, showed spontaneous descent, but at later follow-up again proved to have a testis in a suprascrotal position requiring surgery.

Clinical Definitions

The patient was examined in the supine position with the legs slightly bent. We ascertained the position of the testicle (using the middle of the testis as a reference point for each position) at 1 of 3 levels according to the following: (1) suprascrotal but still palpable, (2) located in the upper portion of the scrotum, or (3) in the lower portion of scrotum. If a testicle spontaneously assumed a suprascrotal position and could not be pulled down into the scrotum, we categorized this as undescended testis. If a testicle in a suprascrotal position could be pulled down into the scrotum but did not remain there after ~30 seconds of traction, we also defined this as undescended testis. If it remained in the upper or lower scrotum position for ~≥10 seconds after the traction was released, it was defined as a retractile testicle. The same pediatric urologist (C.K.) carried out >95% of the clinical examinations.

Ultrasonography

The testicular volume of the retained and scrotal testes was determined with high-resolution ultrasound scanners at ages 0 to 3 weeks, 6 months, and then yearly up to 5 years of age (all time points ±2 weeks). The examination included the lower abdomen, inguinal, and scrotal regions bilaterally. Both sides were compared regarding testicular position, size, and intratesticular morphologic changes. Testes were scanned in axial and longitudinal planes, and at least 3 measurements in each plane were recorded. After the examination, the examiner reviewed the printouts and the largest measurements were selected. Testicular volumes were calculated using the approximation for a prolapsed ellipsoid ($V = \pi/6 \times L\ [\text{length}] \times [\text{width}] \times [\text{height}]$). One single experienced pediatric radiologist performed the majority of the ultrasound procedures. Some patients did not have all scheduled ultrasound examinations because they missed appointments, were ill, or came too late to the appointment.

Ethics

All parts of this study were approved by the Committee for Ethics in Medical Research at the Karolinska Institutet.

Statistical Analyses

The statistical analyses were performed by using the standard statistical package SPSS, version 15.0 (SPSS Inc, Chicago, IL). Results are expressed as mean ± SD unless otherwise specified. Due to skewed distributions of testicular volumes, statistical tests were performed by using nonparametric tests of Wilcoxon type. For the analyses of trends and due to missing values, the data were also analyzed with a generalized linear model for longitudinal data using the program PROC MIXED in SAS. Due to skewed distribution of residuals, the logarithm of testicular volumes were analyzed. The missing values were assumed to be missing at random. A 2-sided $P < .05$ was considered significant.

RESULTS

Spontaneously Descended Testes

Eighty-two percent (58/71) of the testes that descended (and remained in the scrotum during follow-up) had done so between 0 and 3 weeks and 2 months of age. An additional 10% (7/71) descended between 2 and 6 months, and 8% (6/71) descended between 6 months and 1 year.

Ascending Testes

In the 20 (22%) of 91 boys with spontaneous descent who on subsequent follow-up again showed a suprascrotal position of the testis, ~85% (17/20) had descended from the retained position within the first 6 months of life. In 25% (5/20), the testes were again found to be suprascrotal at examination at 1 year, and the rest (15/20), between age 1 and 5 years. These boys were referred for surgery when the ascent was detected.

Comparative Growth of the Spontaneously Descended and the Surgically Treated Testes

Results from comparing growth of the scrotal ("normal"), the spontaneously descended, and the early (9 months) and late (3 years) surgically treated testes from birth to 5 years of age are shown in Fig 1 and Table 1.

The testicular volume of the scrotal ("normal") testis did not differ at any time point when comparing the 3 groups.

At birth, the mean volume of the retained testes was the same in all groups. At 6 months, the spontaneously descended testes were marginally (but not significantly) larger than those that were still retained. The scrotal testis was always larger than its retained or originally retained counterpart.

There was a significant difference in the testicular volume between the early and late treated group from age 2 years and

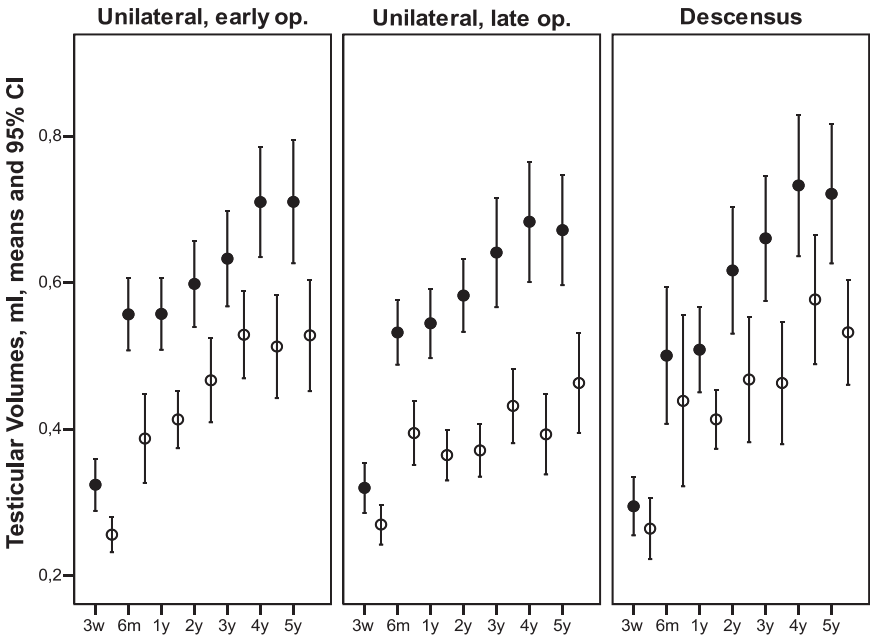

FIGURE 1
Cross-sectional data: The testicular volumes of the retained (open circles) and scrotal (filled circles) testes from birth until 5 years of age. From left to right: early treated (op.) group (9 months), late treated group (3 years), and the spontaneously descended group. Mean and 95% confidence intervals (CI) are shown.

onward, whereas there was no significant difference between the group with spontaneous descent and the group who was treated early, at any age. However, the testes that descended spontaneously were significantly larger than those belonging to the late treated group at ages 2, 4, and 5 years.

Ratios Between Retained and Scrotal Testes at Different Ages

The ratios between the spontaneously descended, early treated, and late treated testes and their scrotal counterparts from birth to 5 years of age are shown in Fig 2 and Table 1. The ratio provides a direct comparison of the 2 testes for the individual boy and thus is an index of the degree of growth deficit of the spontaneously descended testis. The development with increasing age can be expressed as a positive or negative slope of the ratio.

There was a significant difference in the ratio between the early and late treated

TABLE 1 Testicular Volumes of the Retained Testes in the 3 Groups, and Retained/Scrotal Testis Ratios

	Group 1: Unilateral Palpable. Surgery at 9 mo			Group 2: Unilateral Palpable. Surgery at 3 y			Group 3: Spontaneous Descent		
	n	Mean ± SD	*P* Within Group[a]	*n*	Mean ± SD	*P* Within Group[a]	*n*	Mean ± SD	*P* Within Group[a]
Volume of the retained testis, mL			1 vs 2[b]			1 vs 3[b]			2 vs 3[b]
3 wk	50	0.26 ± 0.084	NS	50	0.27 ± 0.096	NS	61	0.26 ± 0.162	NS
6 mo	76	0.39 ± 0.265	NS	67	0.39 ± 0.178	NS	15	0.44 ± 0.211	NS
1 y	70	0.41 ± 0.165	.072	72	0.36 ± 0.147	NS	54	0.41 ± 0.147	NS
2 y	61	0.47 ± 0.224	.001	66	0.37 ± 0.146	NS	34	0.47 ± 0.245	0.008
3 y	52	0.53 ± 0.214	.003	49	0.43 ± 0.177	NS	33	0.46 ± 0.236	NS
4 y	48	0.51 ± 0.243	.001	56	0.39 ± 0.204	NS	26	0.58 ± 0.219	0.001
5 y	44	0.53 ± 0.250	.023	52	0.46 ± 0.245	NS	29	0.53 ± 0.188	0.042
Ratio between the retained and the scrotal testis × 100			1 vs 2			1 vs 3			2 vs 3
3 wk	50	87.0 ± 29.34	NS	49	89.9 ± 27.85	NS	61	98.5 ± 79.82	NS
6 mo	76	76.1 ± 67.89	NS	67	75.1 ± 25.01	0.021	15	86.1 ± 22.08	0.066
1 y	70	78.2 ± 27.36	0.088	72	71.7 ± 28.62	0.051	54	88.0 ± 32.88	0.001
2 y	61	81.8 ± 36.56	0.006	66	64.9 ± 23.98	NS	34	76.4 ± 20.44	0.005
3 y	52	90.2 ± 40.13	0.009	49	73.2 ± 39.59	0.016	33	71.5 ± 26.25	NS
4 y	48	74.4 ± 25.32	0.003	56	62.2 ± 28.84	0.277	26	81.4 ± 28.63	0.001
5 y	44	74.9 ± 22.33	0.094	50	68.7 ± 23.14	NS	29	75.0 ± 18.53	0.078

[a] Wilcoxon signed rank test, difference from "0": 1 vs 2, 1 vs 3, 2 vs 3, *P* values from comparisons between groups, Mann-Whitney tests.
[b] *P* values from SAS PROC MIXED.

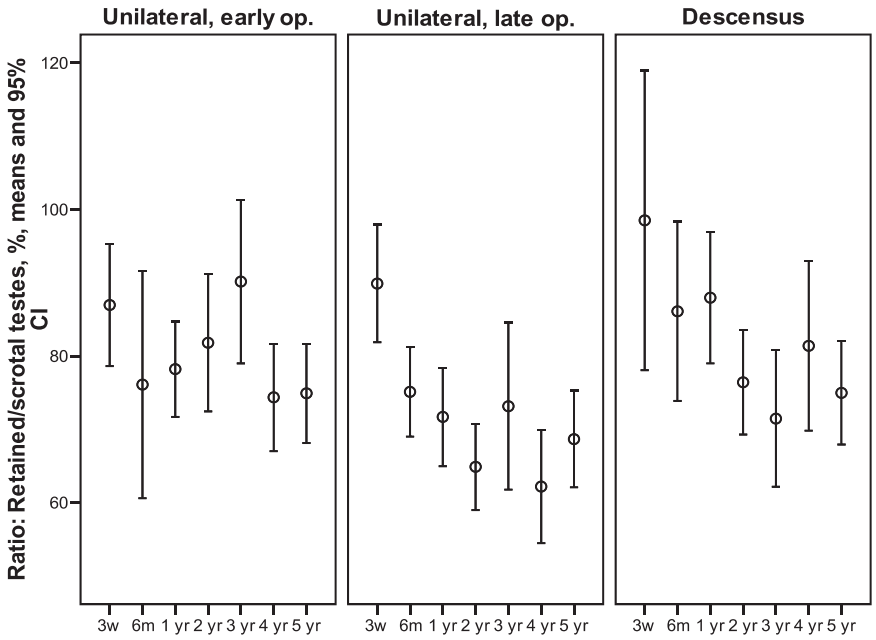

FIGURE 2

Cross-sectional data: The ratios between the previously retained testes and its scrotal counterpart (%) from birth until 5 years of age are shown. From left to right: early treated (op.) group (9 months), late treated group (3 years), and the spontaneously descended group. Mean and 95% confidence intervals (CI) are shown.

groups at ages 2, 3, and 4 years. At ages 6 months and 1, 2, 4, and 5 years, the mean ratio for the boys with spontaneous descent was significantly higher than that for the group who had late surgery. Comparing the early treated with those who had spontaneous descent, we found a significant difference at 6 months, at 1 year (borderline), and at 3 years of age.

Using covariance analysis and data from boys with ≥3 observations over the study period, we showed that the 74 boys operated on at 9 months showed a significant positive slope of the regression line for the ratio retained/scrotal versus age ($P = .013$), whereas the 78 operated on at 3 years of age demonstrated a nonsignificant negative trend ($P = .09$). For the 47 spontaneously descended testes, there was a significant negative regression ($P = .021$).

In addition, the mean slope of the ratios of the group operated on at 9 months differed significantly ($P < .003$) from those operated on at 3 years of age and from the group with spontaneous descent ($P < .001$). This shows that early surgery was superior to late surgery in regard to additional testicular growth, even if the growth rate of the scrotal testes was not reached.

DISCUSSION

In the Nordic countries, a consensus was reached that boys with undescended testes should undergo surgical treatment before the age of 1 year.[28] However, other issues remain controversial, such as the cause and the true incidence of acquired cryptorchidism. Two of the reasons for these uncertainties are that there are few prospective long-term follow-up studies of different treatment modalities and there is a lack of standard definitions. There is, in addition, a lack of long-term prospective studies of boys with spontaneous postnatal testicular descent. In clinical practice, these testes have generally been regarded as normal and, consequently, these boys have been discharged from follow-up.

As discussed previously, studies indicate that highly retractile testes and undescended testes (both congenital and acquired) undergo similar histologic changes. Some investigators advocate a "wait and see" approach until puberty because many of the retractile and acquired testes will descend by puberty.[7–10] However, a considerable number of these testes (both the descended and those that need surgical treatment due to nondescent) were found to be smaller than its scrotal counterpart. Several studies have shown that there is a good correlation between spermatogenic activity of a testis and its volume.[29–31] The older studies measured testicular volume by orchidometer, a method that is difficult to standardize. In the present prospective study, we used ultrasonography, which shows better reproducibility and precision.[32–34]

As shown by our group in previous reports, the longer a testis resides in a suprascrotal position, the more it will be exposed to adverse conditions.[21,29]

Thus, a conservative approach, waiting for acquired forms of cryptorchidism or highly retractile testes to permanently descend into the scrotum, may cause subnormal spermatogenesis. Approximately 22% of the testes that showed spontaneous descent between birth and 6 months later ascended to a suprascrotal position. These boys were surgically corrected when the suprascrotal position was noted during the follow-up. The occurrence of recurrent cryptorchidism thus is also confirmed in our study.

Surprisingly, in boys with unilateral spontaneous descent, the ratio between the volume of the initially retained and the normally descended testes decreased more over the full study period from 6 months to 5 years than the same ratio for both of the surgically treated groups. One hypothesis that might explain this finding is that the surgically treated testes are "fixed" in their position whereas the spontaneously descended testes might temporarily ascend to a suprascrotal position during an ill-defined period of time. As mentioned, we can conclude from this study that these spontaneously descended testes are prone to ascend. We anticipate that the number of ascending testes will increase in this group of boys because the period of maximal retractility will continue beyond 5 years of age, which is the end point of this report.

This study shows that if spontaneous descent occurs, in most cases (>90%) it happens within the first few months of life. In addition, it shows for the first time that in boys with congenital unilateral cryptorchidism and later spontaneous descent, the previously undescended testes prospectively showed impaired growth compared with its scrotal counterpart until at least 5 years of age. Interestingly, already at birth (0–3 weeks) there was a significant difference in mean volume between the retained and the scrotal testes in all studied groups, indicating that the majority of the retained testes were subnormal in this respect already at birth. Additional damage might occur between birth and the spontaneous testicular decent. The volume of the scrotal testes did not differ between any of the groups. However, because this study lacks a control group, it remains to be established whether the testicular volumes are similar to testicular size in boys with no history of cryptorchidism.

We previously showed that orchidopexy at 9 months of age improved the testicular growth compared with those left untreated until age 3 years, although the testes did not fully reach the growth rate of the scrotal testes.[21] In the group who underwent late surgery, growth of the testes during the year after surgery was less than that after orchidopexy at 9 months of age. The precise optimal time for surgery remains to be established.

In conclusion, we have shown for the first time that, contrary to previous beliefs, spontaneously descended testes show impaired growth compared with the scrotal counterpart. Also, we have found a clear relationship between the duration of a suprascrotal position of the testes and testicular growth; the longer the testes reside in this position, the smaller are the testes.

This supports previous proposals that surgical treatment should be performed early in life. About 22% of the testes that descend spontaneously will later ascend and require subsequent surgery. This emphasizes the importance of follow-up of this group of patients.

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