Testing the undescended testis

de Vries, Annebeth

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Testicular microlithiasis in acquired undescended testis after orchidopexy at diagnosis

Evelyn M van der Plas
Annebeth Meij-de Vries
Joery Goede
Laszla M van der Voort-Doedens
Gerda W Zijp
Wilfried WM Hack

ABSTRACT

Purpose
The aim of this study was to observe the prevalence of testicular microlithiasis (TM) in surgically corrected acquired undescended testis (UDT). The prevalence of TM was assessed by ultrasound.

Methods
Boys and young men who had undergone orchidopexy for acquired UDT in mid or late childhood were observed to study the long-term testicular volume. During this examination, the presence or absence of TM was also assessed. TM was defined as echogenic foci without shadowing within the testis parenchyma.

Results
We included 106 patients who had undergone orchidopexy at the Medical Center Alkmaar (1986–1999) and 155 patients who had undergone orchidopexy at the Juliana Children’s Hospital (1996–2009). The majority of patients were white, Caucasian (82%). The median age at follow up, 25.8 years (range 14.0–31.6 years) was higher in Medical Center Alkmaar than in Juliana Children’s Hospital 13.4 years (range 5.1–26.6 years). From 2009 to 2011, these 261 patients (median age 18.9 years) underwent an ultrasound examination. Median follow-up after orchidopexy was 11.3 years (range 1.4–23.5 years); age at orchidopexy ranged from 2.1 to 16.2 years, with a median of 8.5 years. TM was found in 17 (6.5%) patients (median age at follow-up 20.4 years; range 11–28).

Conclusion
No significant association was found with the incidence of TM and the operated testis, the age at orchidopexy or the racial variance (p > 0.05). Orchidopexy at diagnosis for acquired UDT is associated with a 6.5% prevalence of TM in boys and young adults.
INTRODUCTION

Testicular microlithiasis (TM) is characterized by the presence of echogenic foci within the testis parenchyma, measuring 1-3 mm in diameter, without shadowing.¹ TM is usually an asymptomatic finding at ultrasonography and is thought to be the result of microtubular damage, i.e. degenerating cells in the seminiferous tubules. TM has been associated with testicular germ cell tumor and with precursor carcinoma in situ.² The prevalence of TM in asymptomatic boys and young men is racially dependent and reportedly ranges from 2.4% to 5.6%.³⁻⁷ Undescended testis (UDT) may be manifested at birth as congenital cryptorchidism or later in childhood as acquired UDT. An acquired UDT was defined as a UDT that was previously descended. A substantial portion of orchidopexies performed after the age of 2 years are due to acquired UDTs.⁸ In boys with acquired UDT associated with a conservative policy, a TM prevalence of 2.8% was found.⁹ The aim of this study was to determine the prevalence of TM in boys and young men who had undergone orchidopexy at diagnosis for acquired UDT. We hypothesize that the long-term results of surgically corrected acquired UDT may be associated with a higher prevalence of TM.

MATERIALS AND METHODS

Study population
In this study we included two different cohorts of patients who had undergone orchidopexy for acquired UDT at diagnosis in mid or late childhood, i.e. 2-16 years of age. At Medical Center Alkmaar we included 106 patients with 138 acquired UDT, who had undergone orchidopexy (1986-1999) and at the Juliana Children’s Hospital in The Hague we included 155 patients, with 181 acquired UDT, who had undergone orchidopexy (1996-2009).¹⁰,¹¹ The cohort from Medical Center Alkmaar is from an earlier period (1986-1999) because after this period prepubertal surgical intervention was actively withheld in boys with acquired UDT in this hospital, in accordance with the Dutch consensus on non-scrotal testes.¹² As a result, at follow-up these men were older than those operated at the Juliana Children’s Hospital. Both cohorts have been described in detail in earlier publications.¹⁰,¹¹ A UDT was defined as a testis which could not be manipulated into a stable scrotal position in its most caudal location and further
traction on cord structures was painful. Acquired UDT is defined as a UDT previously situated in the scrotum. In this study, acquired UDT was defined as a UDT for which a previous scrotal position had been documented at least twice by youth health care physicians. Exclusion criteria included congenital UDT, e.g. a UDT which had never been scrotal, and retractile testis, e.g. a testis which could be brought into a low stable scrotal position, where it remained after release of the testis until the cremaster reflex was elicited with no shortness of cord structures.

Additional exclusion criteria were previous ipsilateral inguinal or scrotal surgery, laparoscopic orchidopexy and previous hormonal treatment before orchidopexy. Various chromosomal abnormalities have been associated with UDT and/or TM, including Down syndrome, fragile X syndrome, Klinefelter’s syndrome, Noonan syndrome. Therefore we excluded all boys with chromosomal abnormalities or multiple malformation syndromes.

All patients with acquired UDT who underwent orchidopexy at diagnosis were requested to participate in the long-term evaluation.

From 2009 to 2011, all patients underwent one scrotal ultrasound for volume assessment. During this examination, the presence or absence of TM was also determined. Since the prevalence of TM in pediatric, pubertal and young adults may differ, patients were divided into three groups, according to age: 5 to 11 years, 12 to 18 years and older than 18 years.

TM is characterized by multiple hyperechogenic, nonshadowing small foci within the testis parenchyma. The presence of 5 or more echogenic foci, 1 to 3 mm in diameter, in either or both testes was defined as classic TM (CTM). Limited TM (LTM) was defined as fewer than 5 foci.13

**Orchidopexy**

All orchidopexies in both hospitals had been performed under general anesthesia as an outpatient procedure. A classical orchidopexy was started with an inguinal incision. Exploration of the groin took place and if present the open processus vaginalis was separated from the cord structures and ligated. Separation of the cremaster muscle and retroperitoneal funiculolysis were preformed to mobilize the cord. A dartos pouch was created to fixate the testis in the scrotum. The operation was performed by either an experienced pediatric surgeon (Medical Center Alkmaar and Juliana Children’s Hospital) or an experienced pediatric urologist (Juliana Children’s Hospital). The
patients’ medical charts provided information on the indication for orchidopexy, medical history and surgical findings.

Study protocol
In all 106 patients from the Medical Center Alkmaar, the scrotal ultrasound was performed by one physician (JG), and in all 155 patients in the Juliana Children’s Hospital by another physician (EP). All ultrasounds were performed with a 12 MHz linear array transducer (a Falco Auto Image, Falco Software Co (Medical Center Alkmaar) or a Vivid 7 GE Healthcare (Juliana Children’s Hospital). To assess the presence or absence of TM, the scanner was placed on the scrotum while recording transverse and longitudinal images of both testes. Ultrasounds were performed on both testes (in case of unilateral UDT on the previously orchidopexied testis as well as the normally descended testis), documenting the testicle involved and the number of microliths detected. Color Doppler ultrasound of the testis was not performed. A questionnaire was used to inquire about general health, ethnic background, and medical history, including birth weight and gestational age.

Statistical analysis
All data were collected and analyzed with SPSS, version 20.0. Pearson’s chi-squared test was used to analyze the differences between both cohorts in birth weight, gestational age, medication and ethnicity. The independent t-test was used to compare the mean age at orchidopexy, mean age at follow-up, and number of years of follow-up between both cohorts. To adjust for possible confounding factors (e.g. ethnicity, medical history and gestational age), the effect of each of these covariates on the prevalence of TM was analyzed using Pearson’s chi-squared test or Fisher’s exact test (if the expected cell count was <5). For patients with and without TM, the Mann-Whitney U test was used to compare the mean age at orchidopexy, the mean age at follow-up and the interval between orchidopexy and follow-up. Pearson’s chi-squared test was used to compare the TM rate in the different age groups. A p-value of less than 0.05 was considered significant.

Blinded data
Testicular volume and assessment of TM was performed by ultrasound by one investigator (JG) blinded to the first investigator (EP) in 23 patients. The correlation between two investigators was analyzed with Pearson’s chi-squared test.
Ethical approval
The study was approved by the Ethical Committee of Noord Holland and Zuid-Holland West (ref. number: NH 02-099 and ZHW 10-123). Written informed consent was obtained from the patients and/or their parents.

RESULTS

Number of patients
In Medical Center Alkmaar, 106 patients were included with 138 acquired UDT and in Juliana Children’s Hospital 155 patients with 181 acquired UDT. Consequently, a total of 261 patients were included with 319 operated testes. Of these patients, 58 (22%) had undergone bilateral orchidopexy and 203 had undergone unilateral orchidopexy for acquired UDT: 87 left-sided (33%) and 116 right-sided (44%) (Figure 1).

Figure 1  Flowchart of patients (testes) included in this study from Medical Center Alkmaar and Juliana Children’s Hospital

Baseline Characteristics
In both cohorts, the majority was born at term (92%), was Caucasian (82%) and had no significant pathology by history (86%). In Juliana Children’s Hospital, patients were younger at follow-up and more patients suffered from asthma/eczema or allergies and psychiatric problems. These characteristics were analyzed for correlation with the prevalence of TM at follow-up, but no significant effect was found for any of these
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potentially confounding factors (all p-values > 0.05). Table 1 lists the median age at ultrasound, median age at orchidopexy and the interval between orchidopexy and follow-up for both cohorts. All of these three aspects were higher in Medical Center Alkmaar than in Juliana Children’s Hospital (p<0.001).

In Juliana Children’s Hospital more non-Caucasian patients (23%) were included than in Medical Center Alkmaar (4%; p<0.0001). In total 46 patients (18%) were non-caucasian; Asian (n=11; 4.2%), black (n=9; 3.4%), Hispanic (n=1; 0.4%), mixed race (n=25; 9.6%).

Table 1  Baseline characteristics: medical history, age at orchidopexy, age at follow-up, interval between orchidopexy and follow-up (years), and rate of testicular microlithiasis (TM) for Medical Center Alkmaar and Juliana Children’s Hospital separately and combined.

<table>
<thead>
<tr>
<th></th>
<th>Medical Center Alkmaar</th>
<th>Juliana Children’s Hospital</th>
<th>p*-°^- value</th>
<th>Total n=261</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prematurely born (&lt;37 weeks)</td>
<td>8 (8%)</td>
<td>12 (8%)</td>
<td>0.42</td>
<td>20 (8%)</td>
</tr>
<tr>
<td>Low Birth Weight (&lt;2.5kg)</td>
<td>5 (5%)</td>
<td>7 (5%)</td>
<td>0.98</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>4 (4%)</td>
<td>42 (27%)</td>
<td>&lt;0.001</td>
<td>46 (18%)</td>
</tr>
<tr>
<td>Asthma/eczema allergy</td>
<td>3 (3%)</td>
<td>23 (15%)</td>
<td>0.04</td>
<td>26 (10%)</td>
</tr>
<tr>
<td>Psychiatric problems</td>
<td>2 (2%)</td>
<td>8 (5%)</td>
<td>0.76</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Use of medication</td>
<td>3 (3%)</td>
<td>14 (9%)</td>
<td>0.86</td>
<td>17 (7%)</td>
</tr>
<tr>
<td>Urogenital; circumcision</td>
<td>7 (7%)</td>
<td>12 (8%)</td>
<td>0.98</td>
<td>19 (7%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age at orchidopexy (years)</td>
<td>9.3</td>
<td>7.6</td>
<td>&lt;0.001°</td>
<td>8.5</td>
</tr>
<tr>
<td>Median age at follow-up (years)</td>
<td>25.8</td>
<td>13.4</td>
<td>&lt;0.001°</td>
<td>18.8</td>
</tr>
<tr>
<td>Interval (years)</td>
<td>16.2</td>
<td>5.7</td>
<td>&lt;0.001°</td>
<td>11.3</td>
</tr>
<tr>
<td>Prevalence of Testicular Microlithiasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TM - n (%)</td>
<td>5 (4.7%)</td>
<td>12 (7.7%)</td>
<td>0.33^-</td>
<td>17 (6.5%)</td>
</tr>
<tr>
<td>LTM - n (%)</td>
<td>1 (0.9%)</td>
<td>9 (5.8%)</td>
<td>0.05^-</td>
<td>10 (3.8%)</td>
</tr>
<tr>
<td>CTM - n (%)</td>
<td>4 (3.8%)</td>
<td>3 (1.9%)</td>
<td>0.44^-</td>
<td>7 (2.7%)</td>
</tr>
</tbody>
</table>

* Chi-squared test, ° Independent samples t-test, ^ Fisher’s exact test

Testicular microlithiasis

Table 1 also lists the prevalence of TM for both cohorts. Overall, TM was present in 17 patients, yielding a prevalence of 6.5%. CTM was manifest in 7 (2.7%) and LTM in
10 patients (3.8%). There were significantly more cases of LTM in Juliana Children’s Hospital (9/155; 5.8%) than in Medical Center Alkmaar (1/106; 0.9%) (p<0.05).

In all 17 patients, TM was diffusely scattered throughout the parenchyma. TM was bilateral in 11 (64.7%) patients, one of whom had undergone bilateral orchidopexy. In 4 cases (23.5%), TM was present unilaterally in the surgically corrected testis and in 2 cases (11.8%) in the normally descended testis. TM was present in the non-operated testes in 12 of the 28 (42%) with a total prevalence of 12/203 testes (5.9%). Consequently, TM was present in 28 testes and there was no significant association with the operated testis (p=0.8). One patient from Medical Center Alkmaar (aged 26 years) was diagnosed with a testicular germ cell tumor. This patient had bilateral CTM. Pathologic research of the tumor showed a radically resected immature teratoma.

TM was present in 15 of 216 white (7%), 1 of 9 black (11%) and 1 of 11 Asian (9%). The incidence of microlithiases was not significantly racially depended (p=0.3).

**Testicular microlithiasis and age**

For all boys/young adults (n=261), the age at follow-up ranged from 5.1 to 31.6, median age 18.9 years. At follow-up, 133 men were older than 18 years (51%). Median follow-up after orchidopexy was 11.3 years (range 1.4 to 23.5 years); age at orchidopexy ranged from 2.1 to 16.2 years, median 8.5 years.

In the 17 patients with TM, median age at follow-up was 20.4 years (range 11.0 to 27.9 years). The median age at orchidopexy, median age at follow-up, the time interval between orchidopexy and follow-up and testicular volume at follow up were compared between the patients with TM and without TM (Table 2). Men without TM were older at follow up and consequently testicular volume was slightly greater, but no statically significant difference was found (p=0.25). Age at orchidopexy had no influence on the prevalence of TM (p=0.69). The youngest boy diagnosed with TM was 11 years old. The patients were divided into three groups according to age: 5 to 11 years, 12 to 18 years and older than 18 years (Table 3). There was no significant difference in the prevalence of TM between the three groups (p=0.40).
Table 2  Age at follow-up, age at orchidopexy, interval between orchidopexy and follow-up (years) and median testicular volume at follow up for patients with and without testicular microlithiasis

<table>
<thead>
<tr>
<th>Testicular Microlithiasis</th>
<th>present (n=17)</th>
<th>absent (n=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median</td>
<td>range</td>
</tr>
<tr>
<td>Age at orchidopexy (years)</td>
<td>10.4 (4.0 -14.1)</td>
<td>8.4 (2.1 -16.2)</td>
</tr>
<tr>
<td>Age at follow-up (years)</td>
<td>20.4 (11.0 -27.9)</td>
<td>18.5 (5.1 -31.6)</td>
</tr>
<tr>
<td>Interval (years)</td>
<td>10.7 (2.0 -23.5)</td>
<td>11.7 (1.4 -23.5)</td>
</tr>
<tr>
<td>Testicular Volume (ml)</td>
<td>7.9 (0.5 -20.4)</td>
<td>5.8 (0.5-16.3)</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test, # independent samples t -test

Table 3  Prevalence of testicular microlithiasis according to age group

<table>
<thead>
<tr>
<th>Age at follow up (years)</th>
<th>Number of patients (n)</th>
<th>Testicular Microlithiasis present n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-11</td>
<td>47</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>12-18</td>
<td>81</td>
<td>6 (7.4)</td>
</tr>
<tr>
<td>&gt;18</td>
<td>133</td>
<td>10 (7.5)</td>
</tr>
<tr>
<td>Total</td>
<td>261</td>
<td>17 (6.5)</td>
</tr>
</tbody>
</table>

*Chi-squared test p=0.40

Additional findings
At follow-up, 9 patients (3.4%) presented with an extra-testicular varicocele at the ipsilateral side (all left) after orchidopexy for unilateral acquired UDT; 6 of these also had an intra-testicular varicocele. In four other patients (1.5%), an isolated intra-testicular varicocele was observed. In one of these patients with an extra-testicular varicocele at the operated testis, TM was found contralateral.

Blinded data
In 23 boys median age, 14.1 years (range 5.8 to 26.1 years) ultrasonographically measurement of testis volume was performed by a second investigator (JG) blinded to the first (EP). The correlation between both investigators was 0.955 for orchidopexied testis and 0.979 for normally descended testis (p= 0.01). Two of these boys had LTM, as classified by both investigators.
DISCUSSION

This study represents one of the first large prospective ultrasound series examining the prevalence of TM in boys and young men with acquired UDT which was surgically corrected at diagnosis. CTM was found to be present in 2.7% and LTM in 3.8% of patients, whereas the overall TM prevalence was 6.5%.

In pediatric studies, a TM rate of 4.2% has been reported in asymptomatic boys (0-18 years) whereas a higher TM prevalence is associated with a variety of conditions, including cryptorchidism, Klinefelter syndrome, Down syndrome and testicular tumors. For example, in a cohort (mean age 8.8 years) of young boys with Down Syndrome, a TM prevalence of 22.8% was found.

In our cohort, the prevalence in boys aged 12 to 18 years (7.4%) was as high as in young adults, i.e. patients >18 years (7.5%). This finding is in line with Husmann et al who described a two-fold greater incidence of TM in orchidopexied testis two or more years after orchidopexy. Additionally, Riebel et al studied late results after surgically treated cryptorchidism and found a 7% prevalence of TM in boys aged 3 to 13 years; they also found that there was no correlation with the age at surgery. Neither the time interval between orchidopexy and follow-up nor the age at orchidopexy seem to be a factor in the appearance of TM. In a recent study of 320 boys and young men with acquired UDT who had been treated with an expectative policy, a TM rate of 2.8% (n=9; mean age 12.4 years) was found. Of these 9 boys, 2 had mid-pubertal orchidopexy for acquired UDT, whereas in the other 7 spontaneous descent had occurred. The question remains as to whether TM is caused by cryptorchidism itself or that cryptorchidism and TM are manifestations of the same intrinsic tubular abnormality. In addition, it can be speculated that the surgical treatment itself may result in a higher TM rate. Orchidopexy may lead to vascular damage of the testis and ultrasonographic studies suggest that this may be more extensive than previously suspected. Nevertheless, TM is mostly seen bilateral and is also present in asymptomatic boys and young men. There was no significant association with the operated testis or the age at orchidopexy. Peterson et al found that the prevalence of TM in asymptomatic men aged 18 to 35 years was higher in black men (14%). In this cohort the majority of patients was white and TM prevalence was not significantly racially dependent. Although numbers of non-Caucasians included in this study were small. One of our patients had a primary testicular malignancy and bilateral TM. There is
an increase in the prevalence of testicular tumors in patients with TM found.\textsuperscript{17,18} The chance of having carcinoma in situ in subfertile men with bilateral TM increases from 1 to 20%. However, documentation on the risk of testicular malignancy and TM has been inconclusive. In this patient the UDT may have been an additional risk factor.

As seen in this study, TM is already present in boys <18 years of age with acquired UDT after orchidopexy at diagnosis. More research needs to be conducted to compare the prevalence of TM in surgical corrected testes versus acquired UDT after spontaneous descent.

Our findings should be interpreted in the light of their limitations. The follow-up consisted of only one examination and no pre-operative ultrasound. Thus, it was impossible to analyze when the TM had first occurred and whether it was progressing. Although TM may be less common in boys < 10 years, it does occur and it remains unclear in these cohorts whether TM was already present before orchidopexy.

In addition, at follow-up serum levels of FSH, LH and total Testosterone were not measured. Therefore the correlation of TM with hormone levels could not be investigated. The age of onset of TM is largely unknown but may be later in childhood. In Juliana Children’s Hospital, some boys were younger than in Medical Center Alkmaar and may still develop TM at a later age. The progression of LTM to CTM is unknown but may be an important factor as the prevalence of LTM was higher in the younger cohort from the Juliana Children’s Hospital. This limitation in study design may have resulted in an underestimation of the prevalence of TM.

The different ages in various studies reporting on the prevalence of TM should also be taken into account. Moreover, in general, the recognition of TM has increased over the past few years, due to increased awareness of the condition and the use of higher frequency ultrasound. The ultrasounds in both hospitals were performed by two different examiners this may have caused a bias despite the statistically strong correlation between both investigators.

At the Juliana Children’s Hospital more non-Caucasians were included. No association was found between racial differences and the prevalence of TM; nevertheless, only a small number of non-Caucasian was included. Another confounding factor may be the different type of specialist performing the orchidopexy and different surgical techniques may have influenced the TM rate. Although the same inguinal procedure was performed it is expected that surgical technique may differ somewhat among the patients during this study period.
CONCLUSION

In conclusion, orchidopexy at diagnosis for acquired UDT between the ages of 2 and 16 years is associated with a 6.5% prevalence of TM, which is higher than in asymptomatic boys and in acquired UDT associated with a conservative policy. Whether this higher rate is caused by intrinsic factors and/or, at least in some cases, exacerbated by surgical treatment needs to be investigated in future studies.
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References