Pediatr Surg Int (2008) 24:727–730
DOI 10.1007/s00383-008-2143-7

ORIGINAL ARTICLE

Relationship between varicocele grade, vein reflux and testicular growth arrest

Nicola Zampieri · Veronica Zuin · Michele Corroppolo · Alberto Ottolenghi · Francesco Saverio Camoglio

Accepted: 3 April 2008 / Published online: 18 April 2008
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Abstract The development of testicular hypotrophy (or testicular growth arrest) in pediatric patients with varicocele is the first indication for surgery. The aim of this study is to identify the correlation between grade of varicocele, grade of vein reflux and testicular growth arrest. Between 2000 and 2001, we recruited 226 patients affected by varicocele without testicular hypotrophy and with grades 2–3 spermatic vein reflux observed during Doppler velocimetry. Medical examinations carried out every 6 months allowed the assessment of varicocele grade, testicular volume, and grade of vein reflux. Other parameters considered in the study were: mean time of grade deterioration, mean time to onset of testicular growth arrest and the relationship between varicocele grade and testicular growth arrest. Deterioration of the condition was experienced in 92 patients (40%) in which 60 patients showed higher varicocele grades without testicular growth arrest, while 32 patients developed testicular growth arrest. There was a statistically significant relationship between testicular growth arrest and varicocele grades (grade 2 and 3) and between grade of reflux and testicular growth arrest. Although it is not possible to determine which patients will develop testicular growth arrest, the assessment of vein reflux allows the identification of those subjects who may potentially develop such a condition.

N. Zampieri (✉) · V. Zuin · M. Corroppolo · A. Ottolenghi · F. S. Camoglio
Department of Surgical Sciences, Pediatric Surgical Unit, University of Verona, Policlinico "G.B. Rossi", Piazzale L.A. Scuro n. 1-Verona, 37134 Verona, Italy
e-mail: dr.zampieri@libero.it; zampius@libero.it

Keywords Varicocele · Adolescents · Testicular growth arrest · Vein reflux

Introduction

Varicocele is the first cause of male sub-fertility and it is well known for its correlation with testicular growth arrest.

During the past few years, the varicocele was studied in all its etiologic and physiopathological aspects to come to a final conclusion: during childhood, independently from the grade of varicocele, the only objective indication to opt for surgery is a decreased testicular volume ipsilateral to varicocele [1–9].

Clinically it is not yet possible to determine which patients will develop testicular growth arrest on the basis of varicocele grade or the results of clinical-instrumental tests in order to start early treatment.

After monitoring the clinical conditions of patients with varicocele for almost 6 years, the authors in this study consider the possible relationship between varicocele grade, vein reflux and onset of testicular growth arrest.

Materials and methods

Between January 2000 and January 2001, 226 patients aged 10–13 years were attended to in our department where they were observed for "high risk" varicocele (any grade of varicocele with grade 2 or 3 vein reflux without testicular hypotrophy) and consequently enrolled in our protocol.

At our department patients with varicocele are monitored with Doppler velocimetry using the Hirsch classification (Table 1). After identifying the grade of vein

Table 1 Hirsch classification

	Description
Grade 1	No spontaneous venous reflux, but inducible reflux with Valsalva manoeuvre
Pattern 1	Only very little reflux at the beginning of the Valsalva
Pattern 2	Reflux during the full length of the Valsalva
Grade 2	Intermittent spontaneous venous reflux
Grade 3	Continuous spontaneous venous reflux

reflux, each patient was then given different follow-up periods (Table 2).

The protocol was based on our personal experience (data not published), with clinical findings proving a correlation between testicular growth arrest and continuous spermatic vein reflux. The possible correlation between continuous vein reflux (grade 2 or 3) and testicular hypotrophy suggested this clinical-instrumental protocol and a classification of patients with varicocele based on their risk of developing testicular hypotrophy (Table 2).

The following are the inclusion criteria for this study body mass index (BMI) between 18 and 23, weight/age and height/age ratios within normal ranges, non-smokers and regular sport practice (> twice a week), any grade of varicocele never treated before, grade 2 or 3 vein reflux (high risk), absence of testicular hypotrophy, no previous history of surgeries, absence of orchitis or epididymo-orchitis, no scrotal trauma.

Informed consent was obtained from all parents and all patients who completed the assessments with a compliance of 100%. There were no cases of dropouts.

Technique

Patients affected by idiopathic varicocele were treated following a very strict clinical-instrumental protocol to monitor the development of the varicocele over time.

Table 2 Risk classification to develop testicular hypotrophy and follow-up staging

Grade-risk	Description	Follow-up/control
Low	Any grade of varicocele with a grade 1-pattern 1 vein reflux without hypotrophy	1 year
Medium	Any grade of varicocele with a grade 1-pattern 2 vein reflux without hypotrophy	1 year
High	Any grade of varicocele with a grade 2 or 3 vein reflux without hypotrophy	6 months
Critical	Any grade of varicocele and reflux with hypotrophy	Surgery

This included the assessment of varicocele grades according to Dubin and Amelar's classification, Doppler velocimetry of the genital venous system to identify the grade of reflux and testicular US to measure all 3 diameters of the gonad to assess its volume.

Doppler velocimetry was used to find the origin of the spermatic vein reflux following Coolsaet classification, while the different grades of vein reflux were grouped according to Hirsch classification [10–15].

Patients were then grouped independently from varicocele grade into four groups according to the grade of vein reflux and their testicular volume (Table 2). Ultrasounds were performed with Siemens Sonoline Elegra Ultrasound Imaging System, with 5–10 MHz probes. With testicular US, clinicians can assess patients' testicular volume and parenchymal echostructure.

In this study, US tests were performed by the same radiologist and testes were scanned with the same instrument described before using a 7.5-MHz probe. Measurements of testicular length, width, and height were obtained by using electronic callipers. The figures obtained were then substituted into the formula of a prolate ellipsoid to estimate the testicular volume [Vol (ml) $= 0.523 \times L \times W \times H$] [9, 16–21].

According to studies by different authors, differences in the volumes of the two gonads between 20 and 30% indicate ipsilateral testicular growth arrest. In this study, a 20% decrease in gonadal volume was considered significant [22, 23].

Following the study protocol, all patients with "high-risk" varicocele were observed every 6 months, assessing their varicocele grade, grade of vein reflux and testicular volume.

Mean time of deterioration (increase in varicocele grade for grades 1 and 2) together with the onset of testicular growth arrest (independently from varicocele grade), and the correlation between testicular growth arrest and grade of reflux (2 vs. 3) were also considered in the study.

Surgical correction of varicocele was suggested only to patients developing testicular growth arrest.

Testicular catch up after surgery during follow-up was also considered.

Statistical analysis was performed using the chi-square test and Fischer exact tests. P value less than 0.05 was considered significant for the correlation between the variables.

Results

Between January 2000 and January 2001, 226 patients aged 10–13 years with "high risk" varicocele were recruited in the study. At present, all 226 patients are aged between 16

and 19 years and, independently from the treatment received (surgical or non-surgical), and are still attending follow-up visits at our department. All data collected are monitored and recorded on an electronic database. Before each visit patients are contacted by phone. For this reason compliance for this study is 100%.

Among all "high-risk" patients observed during the study period (2000–2001), 52 had grade 1 varicocele, 100 had grade 2 varicocele and 74 showed grade 3 varicocele.

Follow-up involved clinical and radiological tests every 6 months. During this period, 92 patients (40%) showed a deterioration in their condition: 31(59%) of patients with grade 1 varicocele, 42(42%) patients with grade 2 varicocele and 19(25%) with grade 3 varicocele. For grade 3 varicocele deterioration was the onset of testicular growth arrest.

In 60 cases out of 92, varicocele grade worsened without developing testicular growth arrest; the remaining 32 (14%) cases showed onset of testicular growth arrest.

Mean time of deterioration of the condition and varicocele grade

Mean time of deterioration of the condition was 30 months (27 ± 4). It was 1 year for two patients only, both affected by grade 3 varicocele, and 4 years for one patient affected by grade 2 varicocele. Patients with grade 1 varicocele showed a mean time of deterioration of 28 months (26 ± 2), while for patients with grade 2 varicocele the mean time of deterioration was 31 months (30 ± 3). Patients with grade 3 varicocele showed a deteriorated condition after 29 months (26 ± 4).

Testicular growth arrest and varicocele grade

Thirty-two patients developed hypotrophy; 13 patients with grade 2 varicocele and all deteriorated patients with grade 3 varicocele (19 patients). No patients affected by grade 1 varicocele developed testicular growth arrest. Two of the patients with grade 2 varicocele with testicular growth arrest had grade 1 varicocele at the beginning of the study. There is therefore a statistically significant relationship between varicocele grade (2 and 3 vs. 1) and development of testicular growth arrest ($P < 0.05$).

Testicular growth arrest and time of onset

Mean time of onset of testicular growth arrest was 29 months (27 ± 3), for subjects with both grade 2 and 3 varicocele. There was no statistical relationship between mean time of onset of testicular growth arrest and varicocele grade. These parameters should be considered as indicative, because it is not possible to know the pre-study condition.

Testicular growth arrest and grade of reflux

Among all patients with "high risk" to develop testicular growth arrest, 18 had grade 2 vein reflux while 14 had grade 3 vein reflux. There was not a statistical difference ($P > 0.05$).

During the follow-up 22 (68%) of treated patients (32) showed normalization (compared with the right side) of testicular volume. This finding was not correlated with surgical procedure or age at surgery.

Discussion

Varicocele is a developmental congenital disease, usually diagnosed during adolescence. Lesions associated with this condition are considered irreversible. Its correction is therefore necessary to avoid damage to the tissues of the affected testis. [24]

Although the study group included only patients affected by "grade 2 or 3 " vein reflux, the authors observed also "medium and low risk" patients with "grade 1-pattern 1 or 2" vein reflux. These patients were not considered for this study in order to have comparable inclusion criteria. Patients affected by any grade of varicocele but with "grade 1-pattern 1 or 2" vein reflux never showed testicular growth arrest, unless their condition developed towards a "grade 2 or 3" vein reflux.

At present it is not yet clear how to monitor and manage subjects affected by this condition although some articles reported in literature correlate varicocele to morphometric parameters, such as body mass index and pubertal development stage. They also try to identify subjects who need early intervention through the analysis of such parameters. [25–28]

Data collected during the study shows: (1) varicocele is a developmental condition clinically related to pubertal development; (2) "grade 2 or 3" vein reflux are related with testicular growth arrest but nor grade 2 or 3 are strictly correlated with it; (3) patients with grade 1 varicocele will not develop testicular growth arrest if the grade remain unchanged over time; (4) neither the deterioration of varicocele grade nor the onset of testicular growth arrest could be related to the passing of time.

For all these reasons, the clinical development of testicular growth arrest in patients affected by varicocele could be the following: peripubertal adolescent with grade 2 or 3 varicocele and "grade 2 or 3" vein reflux (high risk). These patients will develop testicular growth arrest in 14% of cases. In this paper, the authors focus on the correlation

between grade of varicocele, vein reflux and testicular growth arrest without considering the length of time necessary to develop testicular growth arrest, since this parameter could be assessed only with longitudinal study starting from early infancy (i.e. 7–8 years).

In this study, "high risk" patients included patients with grade 1 varicocele. Although it was suggested that these patients would not develop testicular hypotrophy, it is necessary to closely observe and monitor the possible evolution of this condition towards higher grades with short-term control visits (i.e. every 6 months).

Should further studies confirm these data, it will be possible to confirm that the risk associated with varicocele depends on the grade of both varicocele and vein reflux. The authors therefore believe that it is necessary to closely and constantly monitor this condition through clinical and radiological exams, including a clinical evaluation (to assess its grade), Ultrasounds (to assess its volume) and Doppler velocimetry (to assess the grade of vein reflux). For "high risk" patients, tests were performed to assess varicocele grade and testicular volume only, since there were no reports of cases showing variations of grade of vein reflux (i.e. a grade 2 or 3 vein reflux turning into grade 1).

The Authors also believe that it is necessary to carry out further multicentre studies to develop better comparability when classifying patients affected by varicocele. This would help identify subjects who need early treatment.

Acknowledgments The Authors thank Dr. ssa Cecilia Zampieri, PhD, University of Verona, for her assistance in collecting the results and for the statistical analysis.

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