Gonadal infection: a risk factor for the development of adolescent varicocele

Hassan El-Tatawy, Ahmed M. Elsakka, Ahmed Tawfik, Ahmed Ghaith, Tarek A. Gameel and Mohamed G. Soliman

Objective **The aim of this study was to determine whether a relationship between previous gonadal infections and adolescent varicocele occurrence exists.**

Patients and methods **All adolescents who presented with varicocele at Tanta Urology Department during the period from January 2006 to March 2011 were included in this study. Patients were evaluated for age, clinical presentation, previous history of epididymitis or epididymo-orchitis, laterality, and grading of varicocele. Examination of testicular consistency and ultrasound measurement of testicular volume were carried out for all patients to define those with testicular atrophy.**

Results **Sixty-three boys were included in this study. The mean patients' age was 15.6 years (range: 10–18, SD; 1.6 years). Twenty-nine (44.4%) boys had signs of testicular atrophy (testes are soft in consistency with ultrasound-detected volume smaller than that normal for age) either unilateral or bilateral. About 28.6% of patients (18 boys) had a history of epididymitis or epididymo-orchitis either associated with mumps or of unknown etiology. Of those patients, six boys had previous history of single attack, 10 boys had two attacks, and two boys had more than two attacks of epididymo-orchitis. A significant positive correlation was seen between the incidence of epididymo-orchitis attacks and the grade of varicocele ($r_s = 0.63$, 95% confidence interval: 0.21–0.85, $P < 0.05$). Patients with past history of epididymo-orchitis were significantly more liable (4.1 times) of developing testicular atrophy as compared with those without a history of epididymo-orchitis (95% confidence interval: 1.517–11.097, $P < 0.05$).**

Conclusion **History of epididymo-orchitis is significantly a potential risk factor for the development of adolescent varicocele with subsequently higher risk for testicular atrophy. We advise routine ultrasonographic examinations in patients with previous history of epididymo-orchitis both for possible early detection of varicocele and to avoid testicular atrophy in this cohort of patients. However, more studies on a larger scale are still warranted.** ***Ann Pediatr Surg*** **13:213–216 © 2017 Annals of Pediatric Surgery.**

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Introduction

Varicocele is defined as abnormal tortuosity and dilatation of the pampiniform venous plexus within the spermatic cord. The interest in varicocele could be attributed mainly to the fact that it is the leading cause of male subfertility [1].

Varicocele is seen in ~40% of male population suffering from primary infertility. In those patients, abnormal semen parameters are seen in 25% of them (as compared with only 12% in fertile population) [2]. Several theories were claimed as causes of varicocele, including anatomical factors of draining testicular vein, adrenal metabolites, and congenital absence of venous valves [3].

The associations of adolescent varicocele with different somatic parameters such as height, BMI, suprapubic hair distribution, and testicular volume were documented in many literature studies [4–6]. However, to the best of our knowledge, the association between varicocele and testicular/epididymal infection was not studied before in humans. Doppler ultrasound studies of epididymo-orchitis patients showed that these conditions have increased blood flow to the gonads [7]. This effect carries the theoretical hazard of increased drainage through the developing pampiniform plexus. In this work we will try to find whether there is an association between adolescent varicocele and previous gonadal infections.

Patients and methods

After being approved by our institutional review board, all young boys (younger than 18 years of age) who presented with varicocele as outpatients to Tanta Urology Department between January 2006 and March 2011 were included in this study.

Detailed personal, family, and medical data were discussed with all patients and their parents. Previous incidence of red, hot, and painful scrotum was stressed in all patients' history. Clinical examination and grading of varicocele were performed for by the same doctor for all included patients. Clinically, we used varicocele grading system as follows: grade I (palpable only during Valsalva maneuver), grade II (palpable at rest), and grade III (palpable and visible at rest or appear as a bag of worms) [8].

Exclusion criteria included boys with secondary varicocele, congestive heart problems, undescended testicles or those boys with previous history of inguinal, testicular, or scrotal surgeries.

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Evaluation parameters included patients' age, clinical presentation, and previous history of epididymitis or epididymo-orchitis (including those associated with mumps), laterality, and grading of varicocele.

Examination of testicular consistency and ultrasound measurement of testicular volume were carried out for all patients to define those with testicular atrophy.

In patients with bilateral varicocele, the grade of varicocele was adopted as the grade of the more affected side. Cases were considered as having atrophic testes if he has either ipsilateral or bilateral soft testes.

For those adolescents with high-grade varicocele who underwent surgical repair (through inguinal approach), the excised vessels were examined histologically using standard hematoxylin and eosin stain. Attention was paid for the presence of any inflammatory cellular infiltration around the excised vessels.

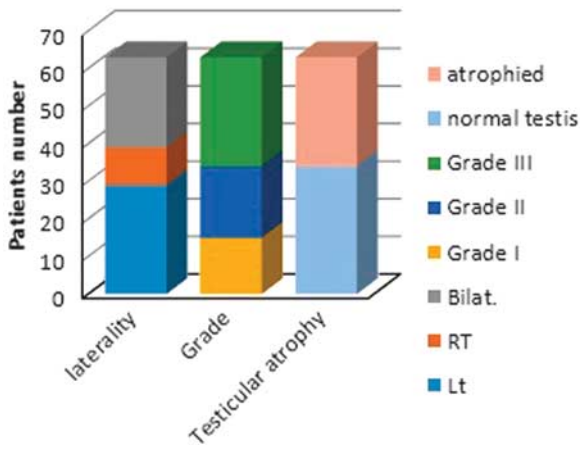
Statistical analysis

Data were organized, tabulated, and presented as % and mean ± SD. Correlation studies were conducted using nonparametric spearman correlation, whereas odds ratios were evaluated using Fisher's exact test. Significance level was considered at P less than 0.05.

Results

A total number of 63 boys were included in this study. The mean patients' age was 15.6 years (range: 10–18, SD: 1.6 years). Twenty-nine (46%) boys were presented with left-sided varicocele, 10 (15.9%) boys with right-sided varicocele, and 24 (36.5%) boys had bilateral varicocele. As regards varicocele grades, 15 (23.8%) boys presented with grade I varicocele, 19 (30.2%) boys presented with grade II varicocele, and 29 (46.03%) boys had grade III varicocele. Twenty-nine (44.4%) boys had signs of testicular atrophy (testes are soft in consistency with ultrasound-detected volume smaller than normal for age), whereas the remaining 34 patients had normal testes (Fig. 1).

Fig. 1



Clinical data of the patients. Bilat., bilateral; Lt, Left; RT, right.

About 28.6% of patients (18 boys) had previous history of epididymitis or epididymo-orchitis either associated with mumps or of unknown etiology. Of those patients six boys had previous history of single attack, 10 boys had two attacks, and two boys had more than two attacks of epididymo-orchitis.

A significant positive correlation was seen between the incidence of epididymo-orchitis attacks and the grade of varicocele [$r_s = 0.63$, 95% confidence interval (CI): 0.21–0.85, $P < 0.05$] (Fig. 2).

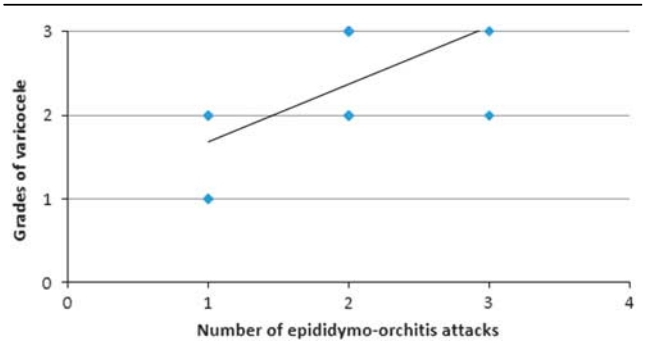
In patients with varicocele, those with past history of epididymo-orchitis were significantly more liable (4.1 times) for developing testicular atrophy as compared with those without a history of epididymo-orchitis (95% CI: 1.517–11.097, $P < 0.05$) (Fig. 3). Only four patients (two patients in each group) out of 29 (13.8%) patients with testicular atrophy had mild-to-moderate testicular pain and the remaining were completely asymptomatic.

Histological evaluation of the excised pampiniform veins was available for 53 specimens from 41 adolescents. Twenty-three specimens belonged to 13 boys with a history of epididymitis or epididymo-orchitis. Histologically, those specimens had much inflammatory cellular infiltration (Fig. 4) than those without a clinical history of epididymitis (Fig. 5).

Discussion

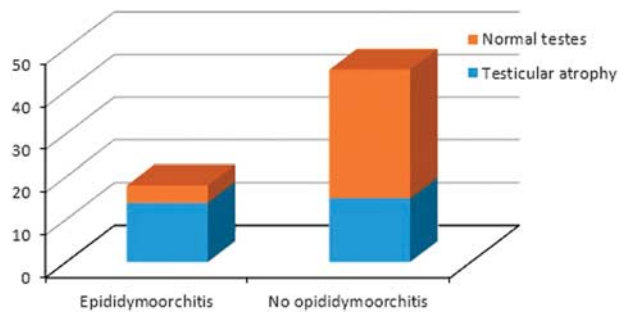
Varicocele has a unique clinical significance as the most common surgically correctible cause of male infertility [9]. Despite decades of studies, the exact etiology of varicocele and its impact on testicular function with

Fig. 2



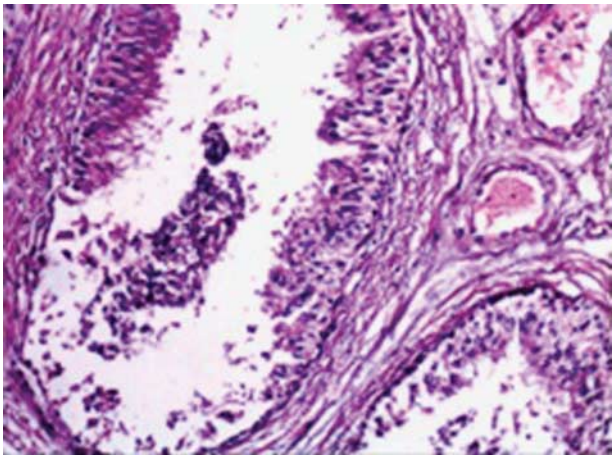
Correlation of epididymo-orchitis to grade of varicocele.

Fig. 3



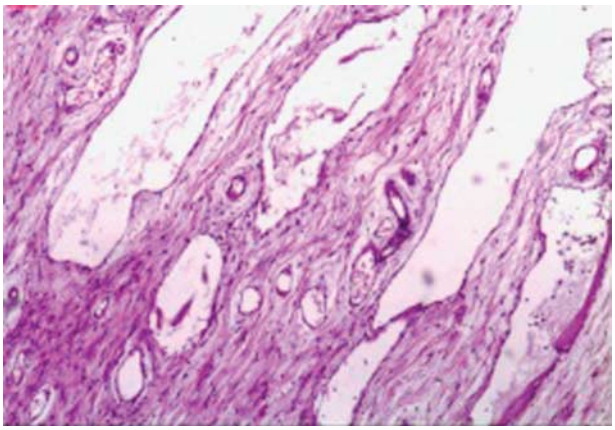
Odds ratio of testicular atrophy.

Fig. 4



Inflammatory cellular infiltration around excised pampiniform veins of an adolescent with past history of epididymitis.

Fig. 5



Dilated noninfilterated excised pampiniform veins of an adolescent without a clinical history of epididymitis or epididymo-orchitis.

subsequent deterioration of male fertility are still unclear [10].

Many theories have been proposed to study the mechanism that causes the disease to affect normal testicular function and causes infertility; however, none has been proved [3]. Elevated testicular temperature, reflux of adrenal breakdown products in the testicular vein, venous stasis, and the resultant hypoxia are possible causes of infertility in varicocele patients.

No single pathophysiological mechanism has satisfactorily accounted for varicocele development, but it seems that the etiology is multifactorial [2].

However, the overall results of all previous mechanisms associated with various factors are increased retrograde blood flow or increased pressure in the pampiniform plexus and internal spermatic vein leading to its dilatation and tortuoisity [11].

Moreover, the presence of hypoxia within the internal spermatic veins of varicocele patients has been recently reported by Lee *et al.* [12,] who demonstrated that there is an overexpression of locally produced hypoxia-inducible factor-1α in varicocele patients. Hypoxia-inducible factor-1α can stimulate the production of vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor-α with the latter considered as the main factor responsible for the increase in the fibrotic tissue of the venous wall in response to hypoxia.

In another series, Tilki *et al.* [13] revealed a progressive reduction in the number of both vasa vasorum and nerve fibers in the wall of large spermatic veins in patients with varicocele, and this finding can explain the cause of hypoxia [14].

Another possible explanation hypothesized that poor venous return, which increases the volume of blood in the testis results in venous stasis, leading to a testicular hypoxia [12].

In an experimental study, Goulestou and colleagues described the features of experimentally induced orchitis associated with *Arcanobacterium pyogenes* and confirmed the pathogenicity of the organism for the testicle. They reported an increase in the ultrasonographic dimensions of the pampiniform plexus [15].

Similarly, in our study, we found that about 28.6% of our varicocele patients (18 boys) had previous history of epididymitis or epididymo-orchitis either associated with mumps or of unknown etiology.

One of the possible explanations of these findings is the theoretical hazard of increased drainage through the developing pampiniform plexus attributed to the increased blood flow to the gonads accompanied the inflammatory process.

The mean platelet volume (MPV) is known as one of the markers that correlate closely with platelet activity and increased in low-grade inflammatory condition [16].

In a preliminary study by Bozkurt *et al.* [17], MPV was evaluated in vascular pathogenetic basis of varicocele. They detected significantly higher MPV values in patients with varicocele. Furthermore, positive correlations were found between MPV and the varicocele grade.

Similarly, in our study, we found a significant positive correlation between the incidence of epididymo-orchitis attacks and the grade of varicocele ($r_s = 0.63$, 95% CI: 0.21–0.85, $P < 0.05$).

One of the possible mechanisms of our hypothesis of both development and increased grade of varicocele associated with epididymo-orchitis may be due to the increase in MPV associated with the inflammatory process.

Varicocele is less common in pediatric population (6% at the age of 10 years); however, the incidence increases in older adolescents to vary between 12.4 and 17.8%, with an average of 14.2% [18].

Interest has been focused on adolescents with varicocele because of the following:

(1) The developmental changes seen at puberty are significantly involved as a predisposing factor for varicocele in adolescent. The predisposing factors for the development of varicocele in the adolescents could be summarized by the incompetent venous valve system or the increased arterial blood flow to the testis at puberty exceeding the venous capacity [18]. The rapid growth could be associated with 'nutcracker effect' and respectively higher hydrostatic pressure in the plexus pampiniformis [4]. Moreover, the developing vessels during infancy and childhood are theoretically liable to dilatation easily on increased venous blood flow or venous pressure [3].
(2) The problem of varicocele in this age group is that it can affect the testicular growth and function [3]. In young population, testicular growth retardation is a very important consequence of varicocele [19]. Moreover, the condition is usually asymptomatic and this carries the risk for silent testicular growth retardation.
(3) Intervention at the proper time with varicocelectomy to correct the condition has been proposed as a therapeutic intervention both to preserve fertility and to preserve testicular growth [20,21].

Another observation in our study was seen histopathologically. It was found that those with a clinical history of epididymitis or epididymo-orchitis, and for unknown cause, had much inflammatory cellular infiltrations around their excised pampiniform veins raising the question about the role of inflammatory infiltrations around the testicular venous drainage as a possible mechanism for development of adolescent varicocele.

In our patients with varicocele, it was found that those with past history of epididymo-orchitis were significantly more liable (4.1 times) of developing testicular atrophy as compared with those without a history of epididymo-orchitis (95% CI: 1.517–11.097, $P < 0.05$). Therefore, a history of epididymo-orchitis may be a second risk factor for the development of testicular atrophy other than varicocele. Our recommendation is to follow this cohort of patients with doppler ultrasound to avoid silent testicular atrophy.

Conclusion

History of epididymo-orchitis is significantly related to the development of adolescent varicocele with subsequently higher risk for testicular atrophy. We propose routine ultrasonographic examinations in patients with previous history of epididymo-orchitis both for possible early detection of varicocele and to avoid silent testicular atrophy in this cohort of patients. However, more studies on a larger scale are still warranted before the final conclusion.

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Study concept and design: Ahmed tawfik, Tarek A. Gameel and Mohamed G. Soliman; acquisition of data: Hassan El-Tatawy, Ahmed M. Elsakka, and Ahmed tawfik; analysis and interpretation of data: Ahmed tawfik and Mohamed G. Soliman; drafting of the manuscript: Hassan El-Tatawy, Ahmed M. Elsakka, and Ahmed Ghaith; critical revision of the manuscript for important intellectual content: Hassan El-Tatawy, Ahmed M. Elsakka, and Ahmed Ghaith; Statistical analysis: Ahmed tawfik and Mohamed G. Soliman; administrative, technical, or material support: Hassan El-Tatawy, Ahmed M. Elsakka, and Ahmed tawfik; supervision: Hassan El-Tatawy, Ahmed M. Elsakka, Tarek A. Gameel and Mohamed G. Soliman.

Conflicts of interest

There are no conflicts of interest.

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