**Abstract**

**Objective:** We intended to revisit aetiology and pathogenesis of varicocele.

**Results:** Several theories were proposed as for the aetiology of left sided varicoceles being commoner than right sided varicoceles such as compression of the left testicular vein by the sigmoid colon, high concentration of adrenaline in the left renal vein causing vasospasms of the left testicular vein, presence of a right angle between the left testicular vein and the renal vein, “nutcracker effect” secondary to a compression of the left renal vein between the superior mesenteric artery and the aorta distal to its confluence with left testicular vein, and the presence of incompetent venous valves of the internal spermatic vein draining the left renal vein causing back flow of the blood. However, these theories were challenged in subsequent studies. Recent studies explored the ultrastructural changes of the pampiniform venous plexus in patients with varicoceles. Histological studies identified changes in the connective tissue density, endothelium and smooth muscle arrangement in these veins. However, the causality of these changes is not yet studied extensively. Genetic studies looking at matrix metalloproteinases synthesis and degradation, inflammation, immune dysregulation or alterations of metabolic pathways are necessary to understand pathogenesis of this clinical entity.

**Keywords:** varicocele, anatomy, histology, pathology

**Introduction**

Varicocele is the abnormal dilatation and the tortuosity of the pampiniform plexus surrounding the testis and dilatation of the internal spermatic vein (1). This clinical entity was first described in the 16th century by the French surgeon Ambroise Pare as dilatation of veins due to sluggish blood flow (2). Majority of the varicoceles (80-90%) are found in the left scrotum; while 30-40% occur bilaterally (3). The prevalence of varicocele is 15% to 19% among males (4,5). Varicoceles contribute to 35% of primary and 80% of secondary subfertility (6). However, aetiology of varicocele is believed to be multifactorial and the exact pathophysiology for this condition is unknown (6).
Main Text

Theories for the left sided varicoceles being commoner than the right sided varicoceles

Several theories have been proposed as for the prevalence of left sided varicoceles being commoner than right sided varicoceles. One reason could be the direct compression of the left testicular vein by the sigmoid colon (7). Another theory was the high concentration of adrenaline in the left renal vein causing vasospasms of the left testicular vein as the left suprarenal vein, similar to the left testicular vein, directly drains to the left renal vein unlike on the right (8). Moreover, presence of a right angle between the left testicular vein and the renal vein may contribute to the pathogenesis of left sided varicoceles. The right angle may lead to an increased hydrostatic pressure leading to dilatation of the left testicular vein (8,9). An alternative theory suggested the change in the normal pressure gradient caused by a “nutcracker effect” secondary to a compression of the left renal vein between the superior mesenteric artery and the aorta distal to the confluence with the left testicular vein (8,10). Nevertheless, in a venography study done on 67 patients with left sided varicocele, 14 did not have a compressive cause (11). Shafik et. al, following measuring the internal venous pressure of renal vein in varicocele and a non-varicocele control group found that there was no significant pressure change in the two groups (10). Findings of this study were confirmed by subsequent studies (9,12).

Another theory on pathogenesis of varicocele was the incompetent venous valves of the internal spermatic vein draining the left renal vein causing back flow of the blood (6). Contrasting this theory, varicocele was observed in patients with or even without the presence of internal spermatic venous valves (12). Out of 659 patients who underwent a venography study with left side idiopathic varicocele, 484 did not have valves while, 172 had competent valves (12). Wishahi et. al, during internal spermatic vein dissection in 70 fresh human cadavers demonstrated the absence of valves, thereby questioned the reflux due to valvular incompetency as a cause for varicocele (13). Retro aortic left renal vein was found to be associated with a high incidence of left sided varicoceles in several studies (14,15). Nevertheless, the studies failed to determine the exact reason for this association.

Ultrastructural changes of the pampiniform venous plexus in patients with varicoceles

Shafik et. al, demonstrated a significant reduction in pressure in the internal spermatic vein of varicocele patients (9 to 18 Hg mm) compared to the non-varicocele (22 to 28 Hg mm) individuals despite the renal vein pressure being almost similar in both groups (10). This highlighted the possibility of microscopic changes in the internal spermatic vessel wall and the pampiniform plexus that could be causing the reduction in the pressure gradient between renal vein and testicular vein.
Over the next few decades, many researchers looking into the microscopic appearance of the testicular veins proposed new theories to explain the pathogenesis of varicoceles. Iafrate et al, conducted a histological analysis of the pampiniform plexus of 30 patients with varicocele and found out that the connective tissue content increased in the outer layers of the vessels with the advancement of severity of varicocele (16). They also found a reduction in the number of vasa vasorum in the adventitia and a reduction in the oblique muscle fibres located between circular and longitudinal muscles (16). In contrast, Tanji et al, reported in 16 patients with varicocele following an electron microscopic examination of the spermatic veins, that there were only two muscle layers (inner circular and outer longitudinal) and according to the severity of varicocele the ratio of smooth muscles to connective tissue did not change (17). Both studies hypothesized the reflux of blood caused the changes in the vessel walls or increase in pressure within the vessel lumen caused the structural changes. Both studies failed to mention why the initial presentation of high connective tissue content was found in the individuals with varicocele compared to the non-varicocele individuals.

An Indian study elicited that significant changes occurred not only in the outer layers of the vessel wall but also in the intimal layers (18). They agreed with Iafrate, with the increase in connective tissue content along with the disease severity advancement. A study on 20 patients with grade three varicocele concluded that the initial damage occurred in the endothelial layer of the vessel, later affected the intimal and muscle layers (19). According to this study, the final step was the replacement of muscle layers by collagen and intimal invagination of media forming pockets.

**Genetic factors contributing to the formation of varicocele**

Raman et al, reported an increased prevalence of varicocele among the first degree relatives (20). Another study verified a prevalence of 45% of varicocele in first degree relatives, compared to the control prevalence of 11% (21). This was further established by a study on 92 patients with a threefold increase in inheritance of varicocele among the first degree relatives compared to the control group (22). Chromosomal abnormalities including Y chromosome microdeletions (23,24), polymorphisms of glutathionine transferase (25) and heat shock protein (26) and acid phosphatase (27) and mitochondrial (28) genes were found to be associated with varicocele in some populations. These genes serve a variety of functions to maintain the integrity of cellular structure (29). Hence, the pathophysiology of the structural derangement could be secondary to differential expression of genes related to matrix metalloproteinases, tissue inhibitors of metalloproteinases, inflammation, immune dysregulation or alterations of metabolic pathways. Nevertheless, functional studies on how these genetic factors cause the development of varicoceles are limited.
Conclusions

Certain anatomical features may predispose the pampiniform venous plexus on the left side to be more prone to varicocele than the right side. The structural changes of the pampiniform plexus may strongly contribute to the pathogenesis of varicocele. However, the underlying mechanisms of how these changes of the microstructural architecture of the pampiniform venous plexus leading to varicocele or the causality remain unclear. Furthermore, considering the presence of a familial inheritance pattern of varicocele, the study of the differential expression of the genes could elucidate the underlying mechanism of the ultrastructural changes.

Dr Yasith Mathangasinghe,
Lecturer,
Faculty of Medicine,
University of Colombo.
yasith@anat.cmb.ac.lk

Submitted by – March 2019
Accepted by – May 2019

References

1. Williams N, O’Connell PR. Bailey & Love’s Short Practice of Surgery. 26 ed: Crc Press; 2013.

2. Mohammed A, Chinegwundoh F. Testicular varicocele: an overview. Urologia internationalis. 2009;82(4):373-9.

3. Leslie SW, Siref LE. Varicocele. StatPearls [Internet]: StatPearls Publishing; 2018.

4. Meacham RB, Townsend RR, Rademacher D, Drose JA. The incidence of varicoceles in the general population when evaluated by physical examination, gray scale sonography and color Doppler sonography. J Urol. 1994;151(6):1535-8.

5. øster J. Varicocele in children and adolescents: an investigation of the incidence among Danish school children. Scandinavian journal of urology and nephrology. 1971;5(1):27-32.

6. Alsaikhan B, Alrabeeah K, Delouya G, Zini A. Epidemiology of varicocele. Asian journal of andrology. 2016;18(2):179.

7. Cleave TL. Aetiology of varicosity. British medical journal. 1972;3(5819):177.

8. Pryor J, Howards S. Varicocele. The urologic clinics of North America. 1987;14(3):499-513.

9. Zerhouni EA, Siegelman SS, Walsh PC, White RI. Elevated pressure in the left renal vein in patients with varicocele: preliminary observations. The Journal of urology. 1980;123(4):512-3.

10. Shafik A, Moftah A, Olfat S, Mohiel-Din M, El-Sayed A. Testicular veins: anatomy and role in varicocele genesis and other pathologic conditions. Urology. 1990;35(2):175-82.

11. Coolsaet B. The varicocele syndrome: venography determining the optimal level for surgical management. The Journal of urology. 1980;124(6):833-8.
12. Braedel H, Steffens J, Ziegler M, Polsky M, Platt M. A possible ontogenic etiology for idiopathic left varicocele. The Journal of urology. 1994;151(1):62-6.

13. Wishahi MM. Detailed anatomy of the internal spermatic vein and the ovarian vein. Human cadaver study and operative spermatic venography: clinical aspects. The Journal of urology. 1991;145(4):780-4.

14. Arslan H, Ettlik Ö, Ceylan K, Temizoz O, Harman M, Kavan M. Incidence of retro-aortic left renal vein and its relationship with varicocele. European radiology. 2005;15(8):1717-20.

15. Karazincir S, Balci A, Gürür S, Sumbas H, Kiper AN. Incidence of the retroaortic left renal vein in patients with varicocele. Journal of Ultrasound in Medicine. 2007;26(5):601-4.

16. Iafrate M, Galfano A, Macchi V, Ejituru E, Sarasin G, Porzionato A, et al. Varicocele is associated with an increase of connective tissue of the pampiniform plexus vein wall. World journal of urology. 2009;27(3):363-9.

17. Tanji N, Fujiwara T, Kaji H, Nishio S, Yokoyama M. Histologic evaluation of spermatic veins in patients with varicocele. International journal of urology. 1999;6(7):355-60.

18. Zaidi MT, Arshad M, Khan AA, Vasanwala S. A histoarchitectural study of varicocele. Biomedical Research. 2014;25(1).

19. Musalam AO, Eid RA, Al-Assiri M, Hussein MRA. Morphological changes in varicocele veins: ultrastructural study. Ultrastructural pathology. 2010;34(5):260-8.

20. Raman JD, Walmsley K, Goldstein M. Inheritance of varicoceles. Urology. 2005;65(6):1186-9.

21. Raman JD, Walmsley K, Goldstein M. Inheritance of varicoceles. Urology. 2005;65(6):1186-9.

22. Mokhtari G, Pourreza F, Falahatkar S, Kamran AN, Jamali M. Comparison of prevalence of varicocele in first-degree relatives of patients with varicocele and male kidney donors. Urology. 2008;71(4):666-8.

23. Gökcçe A, Davarci M, Yalçinkaya FR, Güven EO, Kaya YS, Helvaci MR, et al. Hereditary behavior of varicocele. Journal of andrology. 2010;31(3):288-90.

24. Rao L, Babu A, Kanakavalli M, Padmalatha V, Singh A, Singh PK, et al. Chromosomal abnormalities and Y chromosome microdeletions in infertile men with varicocele and idiopathic infertility of South Indian origin. Journal of andrology. 2004;25(1):147-53.

25. Dada R, Gupta N, Kucheria K. AZF microdeletions associated with idiopathic and non-idiopathic cases with cryptorchidism and varicocele. Asian journal of andrology. 2002;4(4):259-64.

26. Tang K, Xue W, Xing Y, Xu S, Wu Q, Liu R, et al. Genetic Polymorphisms of Glutathione S-Transferase M1,
27. Hassun Filho PA, Cedenho AP, Lima SB, Ortiz V, Srougi M. Single nucleotide polymorphisms of the heat shock protein 90 gene in varicocele-associated infertility. International braz j urol. 2005;31(3):236-44.

28. Gentile V, Nicotra M, Scaravelli G, Antonini G, Ambrosi S, Saccucci P, et al. ACP 1 genetic polymorphism and spermatic parameters in men with varicocele. Andrologia. 2014;46(2):147-50.

29. Heidari MM, Khatami M, Danafar A, Dianat T, Farahmand G, Talebi AR. Mitochondrial genetic variation in Iranian infertile men with varicocele. International journal of fertility & sterility. 2016;10(3):303.

30. Sheehan MM, Ramasamy R, Lamb DJ. Molecular mechanisms involved in varicocele-associated infertility. Journal of assisted reproduction and genetics. 2014;31(5):521-6.