

Bull Yamaguchi Med Sch 41(3-4): 67-71, 1994

Clinical and Animal Studies of the Varicocele: Current Concepts and Treatment

Hiroshi Takihara

Department of Urology, Yamaguchi University School of Medicine, Ube, Yamaguchi 755,
Japan

(Received August 31, revised November 24 1994)

Key Words: Varicocele, Germ cell DNA, Flow cytometry, Spermatogenesis, High ligation

Introduction

Idiopathic varicocele was first described in ancient times, and various modes of treatment have been attempted. In 1952, after performing varicocelectomy in a patient with azoospermia, Tulloch¹⁾ reported a rise in the sperm count to $27 \times 10^6/\text{ml}$, and a patient's wife became pregnant 1 year after the operation. Since then, this condition has come to be suspected as an important cause of male infertility.

The pathophysiology of this common condition remains to be fully investigated, and no theory fully explains either its cause or the physiological alterations by which varicocele induces infertility. When a varicocele is present and a chief complaint is male infertility, the pregnancy rate (PR) after surgery has been reported to be higher than with other types of therapy^{2,3)}. Thus, author generally performs high ligation as the treatment of choice for varicocele. This article reviews the author's investigations into the pathophysiology of varicocele, together with the surgical treatment.

Incidence

The incidence of varicocele in healthy males has been reported to be approximately 8 to 23%, with the left side affected in 70 to 100% of cases, the right in 0 to 9% of cases, and both sides in 0 to 23% of cases^{2,3)}.

Varicocele is generally considered to be an important factor in approximately 21 to 41% of infertile males visiting andrology clinics, and from 20 to 25% of these patients eventually undergo varicocelectomy^{2,3)}.

Disorders of spermatogenesis resulted from varicocele

Opinions vary widely as to whether varicocele uniformly affects spermatogenesis. In fact, seminal abnormalities are not observed in the majority of males with varicocele. It has been stated that abnormal spermatogenesis occurs in about one of every five patients with varicocele³⁾ and that no semen abnormalities were detected in 14% of infertile outpatients with this condition³⁾. The other side of this argument is that a fall in relative sperm motility compared with the sperm count has been observed in men with varicocele and normal sperm count. The PR in the spouses of men within a given range of sperm counts who has undergone varicocelectomy was significantly higher than in a corresponding idiopathic infertility group. A slight deterioration of semen analysis or even early endocrinologic testicular failure has been reported in a varicocele group before surgery, compared with a normal control group. Therefore, investigators should be based on the working hypothesis that abnormal spermatogenesis could occur in patients with varicoceles.

During varicocelectomy of left-sided varicoceles in patients with a chief complaint of infertility, bilateral testicular biopsies were performed, and the deoxyribonucleic acid (DNA) content of the testicular tissue was analyzed by flow cytometry (FCM). At the same time, the germinal cell maturity was assessed using Johnsen's score⁴⁾. The testicular size was measured using Yamaguchi Orchimeter (Medox Enterprise Inc., Tokyo, Japan)^{5,6)}.

Varicoceles were classified into grade I (small) to grade III (large). The left testis was found to be smaller than the right testis for all grades of varicocele, and the left testis in patients with grade II and III varicoceles was smaller than those in the normal control group⁷⁾. By contrast, the right testis in patients with varicocele was significantly smaller than those in the normal control group only for grade III varicoceles and a difference in size was seen between grade I and III⁷⁾. Johnsen's mean score is often used as an index of germinal cell maturity⁷⁾. No significant difference in score was noted between the right and left testicles in patients with grade I or II varicocele, whereas significantly lower values were observed in left testicles with grade III varicoceles. Compared with the normal control group, significantly lower values were found only in the left testicles with grade II and in both testicles with grade III varicoceles⁷⁾.

The percentage of haploid cells (%1C), which indicates the spermatid ratio, was significantly lower in the left testicles of patients with all grades of varicoceles compared with the control group. The right testicles of patients with grade I and III varicoceles showed slightly lower %1C values than the normal controls. To summarize, disorders of spermatogenesis, though observed in both testicles, tended to be more severe on the affected side, and with larger varicoceles^{7,8)}.

In most studies of varicocele, the subjects have been infertile. The clinical impression is that most men with this condition is not necessarily infertile. Therefore, establishing whether or not a strict cause-and-effect relationship exists between varicocele and male infertility requires further investigation using

animal model of this condition. To study the effect of unilateral varicocele on the bilateral testicles in an animal model, the changes of spermatogenesis in rat with surgically induced varicoceles were investigated⁹⁾. The same methodology above described were also applied in this study. We found that in rats with varicoceles, the testicular weight, the %1C, and the mean seminiferous tubular diameter decreased in both testicles in contrast to rats undergoing sham operation, with the decrease being greater on the left testicles. These results suggest that unilateral varicocele impairs spermatogenesis in both testicles, with impairment being greater ipsilaterally. Our results based on FCM DNA analysis in human and animal studies confirm a detrimental effects of a unilateral varicocele on spermatogenesis in both testicles.

Mechanisms leading to impairment of spermatogenesis by varicocele

Various possibilities have been hypothesized to explain the impairment of spermatogenesis associated with varicocele, however none has been proven. Through our investigations, the two most possible hypothesis seem to be the testicular temperature elevation hypothesis and the toxic substance reflux hypothesis.

The temperature hypothesis maintains that a left varicocele raises the temperature of both testicles and elevated testicular temperature is known to have an adverse effect on spermatogenesis¹⁰⁾. We have measured the deep testicular regional temperatures in patients with varicocele, infertile patients without varicocele and postvaricocelectomy patients¹¹⁻¹³⁾. No difference was observed in deep testicular regional temperatures in the supine position, however, higher temperatures were revealed in both the right and left testicles in the varicocele group in the standing position. The temperature was highest and the temperature elevation from the supine to the standing position was greatest on the left testis of patients with large varicocele.

A number of researchers have examined the hypothesis that a high concentration of metabolic byproducts from the kidney or

adrenal glands might have an adverse effect on testicular functions. Attentions have been paid to the hypothesis that prostaglandin (PG) E_2 and $F_2\alpha$ formed in the kidneys reflux into the testicles and disorder the testicular functions¹⁴. Our finding that phospholipase A_2 levels in semen decreased significantly after varicocelectomy appears to be consistent with this theory¹⁵. We have cannulated the internal spermatic vein during high ligation for varicocele and collected blood samples with the cannula tip directed toward the kidney. Peripheral vein blood was simultaneously collected and PGE_2 and $PGF_2\alpha$ were measured. Higher levels of PGE_2 and $PGF_2\alpha$ were disclosed in the internal spermatic vein blood than in the peripheral vein blood. At the same time, a significant correlation between PGE_2 and $PGF_2\alpha$ concentrations in the internal spermatic vein blood was observed, further supporting the PG backflow hypothesis. Abnormalities of blood flow because of vasoconstriction induced by PG and inhibition of the action of luteinizing hormone (LH) by $PGF_2\alpha$ acting on LH receptors in the testicles may be one mechanism adversely affecting spermatogenesis in varicocele¹⁶. Moreover, *in vitro* animal experiment performed by the authors¹⁷ has also demonstrated a close relationship between epididymal contractility and PG. Therefore, the possibility exists that sperm transportation and maturation in the epididymis is affected by PG backflow in varicocele.

Long-term effect of the surgical treatment

The long-term effect of the surgical treatment of varicocele vary widely, and this has made it confused to define the clinical significance of this disorder. The ratio of improvement and PR of patient's partners after the surgical treatment has been reported to range from 53 to 92% and 20 to 55%, respectively^{2,3}. These figures can not be accepted unconditionally in view of the spontaneous variations that can occur in semen analysis, as well as differences in the procedures of measurement and assessment of preoperative severity. Surgical treatment (high ligation and embolization) was performed in 335

patients with varicocele and infertility in a multicenter study in Japan involving the following institutions: Kawasaki Medical University, Tokyo Medical and Dental University, Yokohama City University, Chiba University, Toho University, and Yamaguchi University¹⁸ in 1985. Significant improvement was observed in semen analysis, particularly in sperm concentration and sperm motility. The PR of the partners was 23.5% in the treated group and 18.0% in the untreated group. The cumulative PR tended to rise in the treated group 18 to 24 months after the surgical treatment. The PR was significantly higher in the treated group members with sperm concentrations of $10 \times 10^6/ml$ to $40 \times 10^6/ml$ and a sperm motility less than 20%.

To improve the results of treatment, the more precise and noninvasive methods for the diagnosis of varicocele should be established. Recently, author has reported a usefulness of color Doppler ultrasonography¹⁹, deep testicular regional temperature measurement¹¹⁻¹³ and scrotal radioisotope (RI) angiography²⁰ to divide the varicoceles into subgroups to decide the indication for operation and to dignose subclinical varicocele.

Recent clinical data of the authors' large series of varicocelectomy have demonstrated a significantly improved PRs from 429 patients with varicocele over 16 years²¹. The PR of left varicocelectomy group resulted in 71.1% and PR of bilateral varicocelectomy group was 53.2%²¹.

Acknowledgement: Author wishes to gratefully acknowledge and thank Dr. J. Sakatoku, Professor Emeritus of Urology, Yamaguchi University for his conduction and education, Dr. K. Naito, Professor and Chairman of the Department of Urology, Yamaguchi University School of Medicine, for his directions and recommendation, Dr. A. T. K. Cockett, Professor and Chairman of the Department of Urology, University of Rochester Medical Center, for his collaborations, and all the collaborators in Andrology Research Group of the Department of Urology, Yamaguchi University School of Medicine, for their invaluable contributions.

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