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Epidemiology and Natural History of Prostatic Diseases

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Abstract: The understanding of the epidemiology and natural history of a disease strongly contributes to appropriate diagnoses and the selection of optimal therapies. Epidemiological studies reveal that there are a large number of patients with benign diseases, such as benign prostatic hyperplasia (BPH) and prostatitis, and there are also many men who do not visit the hospital but who have lower urinary tract symptoms (ULTS). On the other hand, a substantial percentage of prostate cancer is detected in patients who seek medical care because of LUTS. Studies of the natural history of diseases demonstrate the importance of identifying factors that denote progressive BPH. Better identification of these factors will enable us to individualize treatment in a more effective way. The same is true for prostate cancer. To determine which treatment is best suited to each type of patient, we need to understand the natural history of prostate cancer, including observation. This approach will enable us to tailor individualized treatment.

Key words: Benign prostatic hyperplasia; Prostate cancer; Prostatitis; Epidemiology; Natural history

Introduction

Including prostatic diseases, understanding the epidemiology and natural history of a disease strongly contributes to appropriate diagnoses and the selection of optimal therapies. For example, not all patients with benign prostatic hyperplasia (BPH) are good candidates for surgery. We know from experience that some patients show no progression of lower urinary tract symptoms (ULTS) for over 10 years without surgery. The application of this experience to the entire population of patients with BPH will provide information that may greatly improve our ability to select treatment options.

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 130, No. 2, 2003, pages 225–229).
The Japanese text is a transcript of a lecture originally aired on April 21, 2003, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

This article describes the epidemiology and natural history of BPH, prostate cancer, and prostatitis, as well as suggestions for clinical practice.

Benign Prostatic Hyperplasia

Twenty years ago, the diagnosis of BPH in patients visiting urology clinics was relatively easy because they usually presented highly developed symptoms and signs of BPH, such as severe LUTS, definite enlargement of the prostate, and large amounts of residual urine. Recently, such patients are relatively rare. Most patients have slight or moderate LUTS, with no definite enlargement of the prostate and normal voiding conditions as assessed by uroflowmetry. The diagnosis of BPH, therefore, is not simple.

Because the number of patients with BPH is fairly large, we tend to misunderstand that patients visiting hospitals represent the entire patient population. However, a large number of patients with the disease reflects the presence of a larger number of men with slight LUTS. It is not appropriate to infer the whole picture of a disease from the number of patients visiting hospitals.

Several studies in the last decade have revealed the prevalence of LUTS or the number of men with these symptoms who do not visit hospitals in various parts of the world. In particular, data from population-based or community-based studies provide a relatively accurate measure of prevalence. These studies are considered to produce less biased results than data from health screenings.

According to a community-based study conducted by the authors in Hokkaido, the percentage of men with moderate or severe symptoms was 40% for those aged 50–59, 52% for those aged 60–69, and 63% for those aged 70–79.[1] These percentages were slightly higher than those in the U.S. and similar to those in Korea.[2] These interesting results offer insight into the ethnic differences in symptoms. On the other hand, the percentage of men with a maximum flow rate (Qmax) of 10 m*l*/sec or less, an indication of impaired voiding, was 6% for those aged 50–59, 19% for those aged 60–69, and 42% for those aged 70–79. The percentage of those with a prostate volume of 20 cc or more, an indication of prostatic enlargement, was 34% for those aged 50–59, 39% for those aged 60–69, and 38% for those aged 70–79.

If we tentatively define BPH by the presence of moderate or severe symptoms, a Qmax of 10 m*l*/sec or less, and a prostate volume of 20 cc or more, the percentage of men meeting these criteria is 6% for those aged 50–59, 6% for those aged 60–69, and 12% for those aged 70–79. At least one in 10 men aged 50 or higher, or 1.2 million men in Japan, are considered to have BPH.[2] Because the above definition is fairly strict, we should assume that a larger number of men have BPH.

A substantial number of men who do not seek medical care satisfy the definition of BPH. Why don't these men visit hospitals? The answer lies in the effects of LUTS on QOL and the degree of patient satisfaction. The authors examined the difference between the results of a community-based study (men not visiting hospitals) and the data from patients visiting hospitals. Among men showing a similar degree of LUTS, those with symptoms causing a stronger deterioration in their QOL or a decrease in satisfaction were more likely to seek medical care.[3]

These results suggest that men visiting hospitals show not only higher degrees of symptoms but also stronger effects of symptoms affecting satisfaction regarding urination and QOL. From this observation, we can understand why we see patients with relatively slight symptoms mixed with those with severe symptoms. The key factor is patient QOL or satisfaction regarding urination. Deterioration in QOL or satisfaction prompts a man to consult a physician. This fact should be considered in the initiation of therapy and in the selection of treatment options.

As discussed above, studies on LUTS and the natural history of BPH provide important information in the selection of optimal therapy for individual cases. Past studies on natural history, in particular, natural history before treatment, show that symptoms, prostate volume, and Qmax in the general male population gradually progress with age or over time.[4,5] The next question is what the predictors for progression of voiding condition are. In other words, how can we identify men who are going to receive treatment in the future?

A prospective study in the U.S. reports the association with age, LUTS, prostate volume, and Qmax.[6] For example, men in the general population in the 70–79 age range were found to be at a risk of progression 7-fold more than those in the 40–49 age range. In addition, men showing marked symptoms during the initial examination had a high probability of receiving some form of treatment due to progression of symptoms.

Our 3-year study of the general population also shows that the degree of LUTS at the initial examination was proportional to the probability of men eventually having the surgery for BPH. These results suggest that the progression of LUTS in the general population is closely associated with the degree of symptoms and prostatic enlargement.[5]

What is then associated with post-treatment natural history or clinical course? In a study using transurethral resection of the prostate (TURP) as the endpoint, it was shown to depend on the degree of symptoms at the time of the first examination.[7] When patients with an indication for surgical treatment were followed according to the watchful waiting strategy, the probability of eventual surgery depended on the degree of symptoms at the time of the first examination.

A long-term study on sympathetic α1 receptor blockers (α1 blockers) indicates that the effectiveness of this treatment was lost in about 40% of cases in 4 years, and the loss of efficacy was strongly associated with prostate volume at the time of the first examination.[8] In fact, more than a 2-fold difference was seen in the occurrence of treatment changes between the patients with a prostate volume of less than 40 cc and those with 40 cc or more. If prostate volume affects clinical progress after treatment, it can be inferred that reduction of prostatic enlargement may be meaningful.

Results from the Medical Treatment of Prostatic Symptoms (MTOPS) are currently considered the most important source of information.[9] It has been shown that a combination of α1 blocker and a 5 alpha-reductase inhibitor is the most effective means of preventing the progression of the disease, which was defined as surgery after medical treatment, acute urinary retention, etc. If the progression of BPH is determined by a complex of the degree of symptoms, the degree of prostatic enlargement, and urination conditions, we may expect that α1 blockers that improve symptoms and urination conditions and agents that reduce prostatic enlargement are both effective in controlling the progression of the disease.

We need careful verification of whether or not the above results apply to our patients particularly with respect to the degree of prostatic enlargement. In fact, ethnic differences have been reported to occur in prostate volume and its increase. The authors have also reported some of these differences.[2] If we could generalize the findings from these studies, we would be able to partially predict what initial treatments are best for individual patients. At this point, we have just achieved several rationale for applying the knowledge of the natural history of BPH in the clinical setting.

Prostate Cancer

Epidemiological studies of prostate cancer have shown recent remarkable increases in the number of patients and prevalence. Part of these increases must reflect the improvement in the detection of prostate cancer using prostate-specific antigen (PSA). However, the incidence

itself is considered to be increasing. At present, the age-adjusted prevalence per 100,000 population has increased to about 12, and this prevalence is 2- to 3-fold higher than 20 years ago. This increase in prevalence is anticipated to continue in the future. The prevalence of prostate cancer is predicted to increase at the highest rate among the types of cancer during the 25 years from 1990 to 2015. The death rate has also been increasing steadily since 1990. In 1997, the age-adjusted mortality from prostate cancer was about 5 per 100,000, and the annual number of deaths was greater than 7,000.

Generally, mass screening for prostate cancer detects cancer in 1% of the men, who participate in the screening. This detection rate is clearly higher than that of mass screening for other cancers, such as gastric cancer, lung cancer, cervical cancer, and breast cancer. Because prostate cancer develops in men aged 50 or more, screening targeted at this age group is effective.

In addition, the detection of cancer in men visiting hospitals because of LUTS is also substantial. In our study, 25% of the approximately 300 men seeking medical care for LUTS had abnormal PSA levels, and 25% of the men with abnormal PSA levels had cancer.[10] In the end, cancer was detected in 7% of men seeking medical care for LUTS. Seventy percent of the detected cancer was in the early stages, and this fact emphasizes the importance of detecting prostate cancer in men visiting hospitals because of LUTS. The need for PSA tests for prostate cancer screening in men without symptoms is somewhat controversial. In the case of men visiting hospitals with LUTS, PSA tests are an essential part of the examination to differentiate prostatic hyperplasia and prostate cancer.

The effectiveness of prostate cancer screening has been studied in the U.S. and Europe, and a similar evaluation has been conducted in Japan from last year. The conclusions of this study are awaited with interest.

Like all cancers, the natural history of prostate cancer involves difficult problems. As a result of the progress in the detection of early-stage prostate cancer, it has been pointed out that there are some cases that do not need to be treated immediately. The so-called "watchful waiting" strategy is indicated for such cases.

A paper published last year provides a suggestion in this respect.[11] This study compared radical prostatectomy and watchful waiting in patients of early-stage prostate cancer presenting similar clinical symptoms. The outcome of treatment was better for radical prostatectomy. These results indicate that radical prostatectomy should be the first-line therapy for early-stage cancer. However, this study also demonstrates the presence of cases that can be managed with watchful waiting. It is a challenge for future studies to clarify how we can select such cases and identify the characteristics of patients suitable for watchful waiting.[12]

Prostatitis

The epidemiological studies of prostatitis have been limited until recently. A group led by the National Institute of Health (NIH) in the U.S. developed a scoring system for chronic prostatitis-like symptoms, and an epidemiological study on prostatitis-like symptoms using this scoring system was commenced. The authors produced a Japanese translation of this scoring system, examined its validity, and reported its usefulness in Japan.[13] The Japan Urological Association is now developing the final version of this symptom-scoring system.

A study in an area in Hokkaido using this symptom-scoring system detected chronic prostatitis-like symptoms in 5% of men in the 20–79 age range. A similar study in Canada reports a prevalence of 10%.[14] Although the definition of the presence of symptoms differs slightly, a study in the U.S. reported a prevalence of 16%.[15]

Thus, it is estimated that about 10% of men aged 20 or more in the general population have chronic prostatitis-like symptoms. Including

the study by the authors, several studies have pointed out a larger decline in QOL in patients with chronic prostatitis than those with prostatic hyperplasia. It is, therefore, important to diagnose and treat men with these symptoms.

Little has been clarified with respect to the post-treatment natural history of prostatitis, in particular chronic prostatitis and chronic pelvic pain syndrome, except that we know there are remissions and exacerbations. The reason for this situation is diversity in the causes of this disease and the resulting lack of our ability to provide appropriate treatment. Another reason seems to have been the lack of an established treatment-evaluation system, in particular a symptom-evaluation system. As mentioned above, a symptom-scoring system has been developed, and randomized clinical trials using this system have commenced. We expect to gain a clearer understanding of the clinical course of the disease after treatment in the future.[16)]

Conclusion

The clarification of the epidemiology and natural history of prostatic diseases is essential for the overall understanding of these diseases. Achievements in these fields surely affect the diagnosis and treatment of these diseases. In particular, the introduction of new therapies needs adequate evaluation of the post-treatment natural history or clinical course. A standard therapy may not be established without such evaluation. In addition, the selection of treatment options suitable for individual patients is also important to provide tailored treatment. Studies of the natural history of diseases are essential prerequisites for achieving these goals.

REFERENCES

1) Tsukamoto, T., Kumamoto, Y., Masumori, N. *et al.*: Prevalence of prostatism in Japanese men in a community-based study with comparison to a similar American study. *J Urol* 1995; 154: 391–395.
2) Tsukamoto, T. and Masumori, N.: Epidemiology and natural history of benign prostatic hyperplasia. *Int J Urol* 1997; 4: 233–246.
3) Masumori, N., Tanaka, Y., Takahashi, A. *et al.*: Lower urinary tract symptoms of men seeking medical care-comparison of the symptoms found in the clinical setting and in a community-based study. *Urology*; 62: 266–272.
4) Jacobsen, S.J., Girman, C.J. and Lieber, M.M.: Natural history of benign prostatic hyperplasia. *Urology* 2001; 58 (suppl. 6A): 5–16.
5) Masumori, N., Tsukamoto, T., Girman, C.J. and Jacobsen, S.J.: Natural history of lower urinary tract symptoms of men-results of a longitudinal community-based study in Japan. *Urology* 2003; 61: 956–960.
6) Jacobsen, S.J., Jacobsen, D.J., Girman, C.J. *et al.*: Natural history of prostatism: risk factors for acute urinary retention. *J Urol* 1997; 158: 481–487.
7) Barry, M.J., Fowler, F.L. Jr., Bin, J. *et al.*: The natural history of patients with benign prostatic hyperplasia as diagnosed by North American urologists. *J Urol* 1997; 157: 10–15.
8) de la Rosette, J.J., Kortmann, B.B., Rossi, C. *et al.*: Long-term risk of re-treatment of patients using alpha-blockers for lower urinary tract symptoms. *J Urol* 2002; 167: 1734–1739.
9) McConnell, J.D., Roehrborn, C.G., Bautista, O.M., Andriole, G.L. Jr.; Related Article, Link. Dixon, C.M., Kusek, J.W., Lepor, H., McVary, K.T., Nyberg, L.M. Jr., Clarke, H.S., Crawford, E.D., Diokno, A., Foley, J.P., Foster, H.E., Jacobs, S.C., Kaplan, S.A., Kreder, K.J., Lieber, M.M., Lucia, M.S., Miller, G.J., Menon, M., Milam, D.F., Ramsdell, J.W., Schenkman, N.S., Slawin, K.M., Smith, J.A.; Medical Therapy of Prostatic Symptoms (MTOPS) Research Group: The long-term effect of doxazosin, finasteride, and combinaiton therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003; 349: 2387–2398.
10) Tanuma, Y., Yanase, M., Kitamura, H., Takahashi, A. *et al.*: Detection of prostate cancer in patients presenting with voiding symptoms. *Collected Papers from Grant Studies XVIII*, Kenko Kanri Jigyodan, 2002; 1–5. (in Japanese)

11) Holmberg, L., Bill-Axelson, A., Helgesen, F. *et al.*: A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med* 2002; 347: 781–789.
12) Walsh, P.C.: Surgery and the reduction of mortality from prostate cancer. *N Engl J Med* 2002; 347: 839–840.
13) Kunishima, Y., Matsukawa, M., Takahashi, S. *et al.*: National Institutes of Health Chronic Prostatitis Symptom Index for Japanese men. *Urology* 2002; 60: 74–77.
14) Nickel, J.C., Downey, J., Hunter, D. *et al.*: Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health chronic prostatitis symptom index. *J Urol* 2001; 165: 842–845.
15) Roberts, R.O., Jacobson, D.J., Girman, C.J. *et al.*: Prevalence of prostatitis-like symptoms in a community based cohort of older men. *J Urol* 2002; 168: 2467–2471.
16) Nickel, J.C., Downey, J., Johnson, B. *et al.*: Predictors of patient response to antibiotic therapy for the chronic prostatitis/chronic pelvic pain syndrome: a prospective multicenter clinical trial. *J Urol* 2001; 165: 1539–1544.

Lower Urinary Tract Symptoms (LUTS) in Middle-Aged and Elderly Men

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Abstract: Lower urinary tract symptoms (LUTS) include storage symptoms (previously termed as irritative symptoms), voiding symptoms (previously termed as obstructive symptoms) and post-micturition symptoms. The International Continence Society (ICS) published a new standardization of terminology of lower urinary tract function in 2002. Storage symptoms include increased daytime frequency, nocturia, urgency and incontinence. Of incontinence, stress, urge and mixed incontinence are the major symptoms, and ICS has also defined enuresis, continuous incontinence and giggle incontinence as other types of incontinence. Urgency, with or without urge incontinence, usually with frequency and nocturia, can be described as overactive bladder (OAB) syndrome, urge syndrome, or urgency/frequency syndrome. These syndromes suggest urodynamically demonstrable detrusor overactivity, but may be due to other forms of urethro-vesical dysfunction. ***Overactive bladder*** is an empirical diagnosis used as the basis for initial management after assessing lower urinary tract symptoms, physical findings urinalysis, and other indicated evaluation. Voiding symptoms include slow stream, splitting or spraying, intermittency, hesitancy, straining and terminal dribble. Post micturition symptoms include a feeling of incomplete emptying and post micturition dribble. The "feeling of incomplete emptying" symptom was formerly categorized as either a storage symptom or a voiding symptom, but has been categorized among the post micturition symptoms in the new ICS terminology. "Post micturition dribble" is the term used when an individual describes the involuntary loss of urine immediately after he/she has finished passing urine, usually in men after leaving the toilet. Thus this symptom is not incontinence, and is categorized among the post micturition symptoms.

Key words: Lower urinary tract symptoms; Men; Overactive bladder; Incontinence; International Continence Society

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Introduction

In middle-aged and elderly men, various urination disorders are caused by urinary tract obstruction due to prostatic hyperplasia and other diseases, as well as neurogenic bladder due to neurological diseases such as cerebral infarction.

Urination symptoms caused by these urination disorders are generally referred to as lower urinary tract symptoms (LUTS). As urination disorders are classified into storage disorders and voiding disorders, LUTS are accordingly classified into storage symptoms and voiding symptoms.

The terms related to lower urinary tract function, including LUTS, are defined by the International Continence Society (ICS), and the standard terminology was redefined in 2002.[1] The new definition includes a new category of post micturition symptoms, in addition to conventional storage and voiding symptoms. This article explains LUTS according to the new terminology.

Table 1 Lower Urinary Tract Symptoms: LUTS

I. Storage symptoms
  1. Increased daytime frequency, pollakiuria
  2. Nocturia
  3. Urgency
  4. Incontinence
    (1) Stress incontinence
    (2) Urge incontinence
    (3) Mixed incontinence
    (4) Enuresis, nocturnal enuresis
    (5) Continuous incontinence
    (6) Other types of incontinence [coital incontinence, giggle incontinence]
  5. Bladder sensation [normal, increased, reduced, absence, non-specific]

II. Voiding symptoms
  Slow stream
  Splitting or spraying
  Intermittency
  Hesitancy
  Straining to void
  Terminal dribble

III. Post micturition symptoms
  Feeling of incomplete emptying
  Post micturition dribble

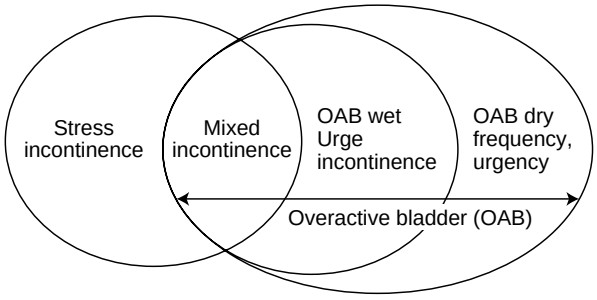

Fig. 1 Storage symptoms and incontinence

Storage Symptoms

Storage symptoms are symptoms occurring in the storage phase, such as increased daytime frequency, nocturia, urgency, and incontinence (Fig. 1). These symptoms were previously called irritative symptoms because they appeared as if resulting from irritation of the bladder. However, the term "storage symptoms" is now preferred because they actually are not related to irritation.[2]

1. Increased daytime frequency or pollakiuria

This refers to an abnormal increase in the frequency of urination. The normal frequency of urination in adults is considered to be 4 to 6 times a day. Hence, a frequency of 8 times or more a day is regarded to constitute increased daytime frequency. The cause of this symptom is the decrease in functional bladder capacity (maximum bladder capacity minus residual urine volume). This may result either from decreased maximum bladder capacity as a result of overactive bladder (see below) or from the decrease in single voided volume reflecting the increase in residual urine.[2]

When an abnormal increase in urine volume (diabetes insipidus) increases the frequency of urination, this condition is called polyuria. Polyuria is defined by a daily urine volume of 2,800 m*l* or more.[3]

2. Nocturia

Nocturia is defined as waking at night to urinate. The ICS standard defines it as rising from sleep to void once or more at night. However, because voiding once at night is not rare in persons aged 50 or more, nocturia is often considered as voiding more than once at night. Nocturnal polyuria needs to be differentiated from nocturia. Nocturnal polyuria is a condition in which nighttime (from 23:00 to 7:00) urine volume is 33% or more (20% or more for young adults) of daily urine volume.[3)]

3. Urgency

Urgency is a sudden compelling desire to void with a feeling that micturition is imminent. The former definition classified urgency into motor urgency associated with overactive contraction of the detrusor muscle and sensory urgency caused by hypersensitivity of the bladder and the urethra in the absence of overactive contraction. However, because the distinction between motor urgency and sensory urgency cannot be shown clearly even by the use of advanced urodynamic tests, the revised terminology does not divide urgency into these types.

4. Urinary incontinence

(1) Stress urinary incontinence

This refers to the leaking of urine that occurs during effort or exertion causing sudden increases in abdominal pressure, such as coughing, straining, laughing, standing up from a sitting position, and lifting heavy objects. A cause of stress urinary incontinence is anatomical abnormalities involving weakening of supporting tissues around the bladder neck and the proximal urethra. Other causes include hypermobility of the fundus of bladder (Types I and II) and neurogenic conditions (intrinsic sphincter deficiency; ISD, Type III).[4)]

Stress urinary incontinence usually occurs in women. It is seen in middle-aged and elderly men after prostate surgery, in particular when the urethral sphincter muscle has been damaged in radical prostatectomy.

(2) Urge urinary incontinence

This refers to incontinence accompanying urgency. The cause is overactive contraction of the detrusor muscle. While detrusor overactivity is usually seen in the supranuclear neurogenic bladder due to cerebral infarction or cervical spondylosis, it also arises from lower urinary tract obstruction due to prostatic hyperplasia and from unknown causes.[4)]

Although the former was called detrusor hypersensitivity and the latter was called unstable bladder in the past, it is difficult to strictly differentiate these 2 conditions. The new definition, therefore, classifies into neurogenic and idiopathic detrusor overactivity (DO). Urge incontinence is the most commonly observed type of incontinence among middle-aged and elderly men.

[Overactive bladder (OAB)]

While detrusor overactivity is considered the cause of increased daytime frequency, urgency, and urge incontinence, the diagnosis of detrusor overactivity requires urodynamic testing to evaluate urination functions.

Diagnosis based on a urodynamic observation may vary depending on whether it is conventional cystometry or a new method such as ambulatory urodynamics (the measurement of intravesical pressure in essentially the same manner as Holter ECG), as well as whether the test is performed by a specialist in urination, a general physician, a technician, or a nurse. In addition, we cannot diagnose OAB with 100% reliability even when advanced urodynamic studies are performed.

Therefore, we need to be able to define conditions considered to arise from overactive detrusor based on symptoms in daily practice. For this reason, the ICS has defined such conditions as overactive bladder (syndrome). OAB is characterized by urinary urgency and typically accompanies increased daytime frequency and nocturia. There are 2 types of OAB: one with urge incontinence (OAB wet) and one without (OAB dry). The ICS considers

OAB to be synonymous with urge syndrome and urgency/frequency syndrome.

These terms are considered to lack scientific significance and should be used for initial micturition management based on empirical diagnosis in daily practice after the evaluation of symptoms and physical findings, and exclusion of organic disorders.[1)]

(3) Mixed incontinence

This type of incontinence is defined by the presence of both stress incontinence and urge incontinence.

(4) Enuresis and nocturnal enuresis

Enuresis is any involuntary urine leakage and usually refers to that occurring at night. Nocturnal enuresis is urine leakage occurring at night.

(5) Continuous incontinence

This is defined as continuous occurrence of urine incontinence. Continuous incontinence is considered the same as what was previously called total incontinence.[2)] In this condition, the bladder lacks the ability to store urine and works only as a channel for urine flow from the ureters to the urethra, resulting in the slow leakage of urine from the external urethral orifice. A congenital anomaly called myelomeningocele sometimes accompanies this condition. The incontinence seen in the cases of ectopic ureteral opening and vesicovaginal fistula is defined as extra-urethral incontinence.[1,2)]

(6) Other types of incontinence

There are other types of incontinence such as coitus incontinence, giggle incontinence, etc.

(7) Incontinence not defined in new ICS terminology

The following types of incontinence were defined in the 1988 terminology but were excluded from the new version:

a. Reflex incontinence: Reflex incontinence is seen in spine diseases at the lumber or higher level without impairment of the sacral micturition center. The patient feels no voiding desire. When a certain amount of urine is stored in the bladder, the detrusor muscle contracts reflexively and causes urine leakage. While this condition with reflex contraction was previously called reflex bladder, it was unified in the above-mentioned category of neurogenic overactive detrusor. Because patients with reflex incontinence often have impairment in coordination between the detrusor muscle and the sphincter muscle of the urethra, they are at an elevated risk of upper urinary tract impairment and urinary tract infection due to high-pressure voiding and residual urine.[2)]

b. Overflow incontinence: Overflow incontinence occurs in cases with urinary retention or a large volume of residual urine. Physical activities that increase abdominal pressure cause overflowing of the urine stored in the bladder. This condition may occur in cases of prostatic hyperplasia developing advanced voiding impairment. Such cases need sufficient attention because there is a risk for upper urinary tract impairment. This condition is diagnosed based on the ultrasound confirmation of the presence of a large amount of residual urine. Treatment consists of urethral catheterization and treatment for voiding impairment.

c. Functional incontinence: Functional incontinence includes incontinence due to difficulty in moving and that due to dementia. Patients with incontinence due to difficulty in moving, patients with motor paralysis, parkinsonian syndrome, bone fracture, arthralgia, etc. feel a voiding desire and want to go to the bathroom, but are prevented from completing voiding actions because they are unable to reach the bathroom in time, assume a voiding posture, or remove their clothes. Incontinence due to dementia may result from disorientation, lack of comprehension, or attention deficit. Patients urinate in corners of rooms, entrance halls, corridors, or other inappropriate places because they do not know the location of the toilet, they do not understand how to use the toilet, they mistake the place for the toilet, they want to attract the attention of caregivers and other persons around them, or they want to embarrass them.

5. Bladder sensation

The new definition by the ICS classifies bladder sensation into 5 categories of normal, increased, reduced, absent, and non-specific.

Voiding Symptoms

Voiding symptoms include difficulties experienced during the voiding phase, such as slow stream, splitting or spraying, intermittency, hesitancy, straining to void, and terminal dribble.

Urinary retention is the condition with a total inability to void or very limited voiding. The former is called complete urinary retention, the latter incomplete urinary retention.

Post Micturition Symptoms

This term was newly defined in the revised terminology. These include symptoms observed shortly after voiding.

1. Feeling of incomplete emptying

While this symptom can be regarded as a voiding symptom (feeling of the presence of residual urine as a result of e.g., prostatic hyperplasia), it can also be regarded as a storage symptom (e.g., bladder irritation due to cystitis or prostatitis). Authors of reports in the past, therefore, classified this symptom into either of these categories. The new terminology classifies it into the new category of post micturition symptoms.

2. Post micturition dribble

Post micturition dribble in men is the dribbling of urine remaining in the urethra after the end of voiding. While "terminal dribble" refers to the dribbling of urine for several seconds or a few minutes at the end of micturition following the main urinary stream, this should be distinguished from post micturition dribble. The volume of dribbling urine is several milliliters at maximum. The urine remaining in the urethra is discharged by the action of the bulbocavernosus muscle. Probably due to the weakening of the contraction of this muscle in those aged over 40, post micturition dribble is not rare in men at these ages.[2] Hence, in contrast with terminal dribble, post micturition dribble is usually not abnormal. Women sometimes experience dribbling shortly after standing up from the toilet.[1]

Lower Urinary Tract Symptom Score

The scoring of symptoms is a useful means of evaluating LUTS, determining severity, and assessing treatment effects. The International Prostate Symptom Score (IPSS) is a scoring system that is most commonly used in prostatic hyperplasia.

The IPSS consists of 3 items regarding storage symptoms (frequency, urgency, nocturia), 3 items regarding voiding symptoms (intermittency, slow stream, straining to void), and an item regarding post micturition symptoms (feeling of incomplete emptying): 7 items in total. Each item is evaluated in a 6-point score from 0 (never) to 5 (almost always). According to the Guidelines on Benign Prostatic Hyperplasia, total scores of 8 or less represent mild symptoms, 9–15, moderate, and 16–35, severe. In addition, a quality of life (QOL) score evaluates the patient's satisfaction with the current urination condition in a 7-point score from 0 (very satisfied) to 6 (very unsatisfied).

Since the presence of symptoms is an essential prerequisite for diagnosis of prostatic hyperplasia, the evaluation of LUTS is considered extremely important.[4] However, the IPSS is poorly correlated with lower urinary tract functions and prostatic obstruction diagnosed based on urodynamic studies (including pressure/flow study). Other problems have also been pointed out, such as that the 6-point scoring in the IPSS is too detailed, the score evaluates only the frequency of symptoms without regarding degree of symptoms, and that the questions (in Japanese translation) cannot be easily understood by Japanese

patients. Because the content of the IPSS is not specific to prostatic hyperplasia, this score can be used to evaluate various voiding dysfunctions including those in women.

Aside from the IPSS, several LUTS scores have been proposed such as the Danish-PSS and the ICS score. Japanese urologists are developing a LUTS score that would be comprehensible to Japanese and correlate with lower urinary tract functions.

Symptom scores and QOL scores for the evaluation of urinary incontinence have also been proposed, including the Urogenital Distress Inventory (UDI)-6 and the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF).[5)]

Points in Interviews with Patients

When we ask a patient about his condition, we need to: (1) clarify whether he has LUTS or not; (2) if there are LUTS, classify them into storage symptoms and voiding symptoms; and (3) ask about the degree of LUTS in detail and score these symptoms. It may seem easy to clarify whether the patient has LUTS or not, but this is actually rather difficult because many patients are not aware of the presence of abnormal symptoms.

Generally, voiding symptoms that have developed chronically are less likely to be realized by patients because distress from such symptoms tends to be relatively mild. On the other hand, patients are usually aware of storage symptoms because they cause distress. To obtain accurate information on incontinence and other storage symptoms, it is advisable to instruct patients to record the time and amount of urination, as well as the time and amount of involuntary urine loss, for several days using frequency volume charts.

REFERENCES

1) Abrams, P., Cardozo, L., Fall, M. *et al.*: The standardization of terminology of lower urinary tract function: report from the Standardization Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; 21: 167–178.
2) Hattori, T., Yasuda, K., Yamahishi, T. *et al.*: *A Handbook on Voiding Dysfunction Due to Neurological Diseases.* Miwa Shoten, Tokyo, 1998; pp. 50–66. (in Japanese)
3) Yasuda, K., Igawa, Y., Yamashita, T. *et al.*: *Medical Treatment of Voiding Dysfunction.* Miwa Shoten, Tokyo, 2000; pp. 136–172. (in Japanese)
4) van Kerrebroeck, V., Abrams, P., Chaikin, D. *et al.*: The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; 21: 179–183.
5) Goto, M., Donovan, J., Corcos, J. *et al.*: Symptoms of urinary incontinence — QOL questionnaire: Scored ICIQ-SF (International Consultation on Incontinence Questionnaire-Short Form). *Journal of Japan Neurogenic Bladder Society* 2001; 12: 227–231. (in Japanese)

Clinical Use of Prostate Specific Antigen (PSA)

JMAJ 47(12): 549–554, 2004

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Abstract: Like other countries, Japan is recording a rapid increase in the incidence of prostate cancer. The use of serum PSA (prostate specific antigen) measurement as a blood marker for prostate cancer has become widespread. Higher levels of PSA are associated with a higher probability of a diagnosis of prostate cancer. Needle biopsies detect prostate cancer in 20–30% of cases with PSA levels of 4.1–10 ng/m*l*, and 30–50% or more of cases higher than 10 ng/m*l*. All cases showing PSA levels of 4.1 ng/m*l* or more should be referred to specialist urologists, as well as those showing PSA levels of 4.0 ng/m*l* or less and positive findings on digital rectal examination. However, PSA also increases in other conditions such as benign prostatic hyperplasia, prostatitis, and urinary retention, and this fact needs careful attention. In addition, there is a risk that administration of antiandrogen may lower PSA levels and mask the presence of prostate cancer. So-called gray-zone cases with PSA levels of 4–10 ng/m*l* present a problem of differentiation from benign prostatic hyperplasia. Improvement in accuracy has been attempted with various approaches, such as PSA density, PSA free/total ratio, PSA velocity, and age-specific PSA reference ranges. In observation after the treatment of prostate cancer, PSA is useful for the early diagnosis of recurrence and relapse.

Key words: Prostate cancer; Prostate specific antigen (PSA); Blood marker; Screening

Introduction

In the past, Japan had a lower incidence of prostate cancer than European countries and the U.S. However, Japan is also recording a rapid increase in the incidence of prostate cancer, reflecting the aging of society and changes in lifestyle.

The use of the measurement of prostate specific antigen (PSA) as a blood marker for

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prostate cancer has become widespread.[1] As a result, physicians other than specialist urologists are now required to measure serum PSA and appropriately manage patients showing high PSA values.

This article outlines the characteristics and significance of PSA, as well as key points in measurement and clinical action.

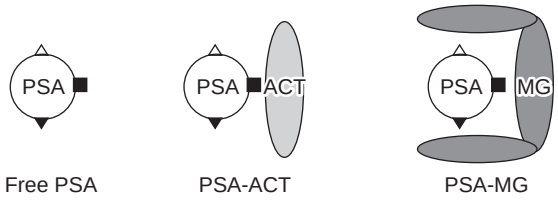

Fig. 1 Molecular forms of PSA in blood
Free PSA
PSA-ACT: α1-antichymotrypsin-bound PSA
PSA-MG: α2-macroglobulin-bound PSA
□△▲: Epitopes

Characteristics of PSA

1. Characteristics of PSA protein

PSA is a glycoprotein occurring abundantly in seminal fluid. It has a molecular weight of about 34,000, and consists of 240 amino acid residues and 4 sugar chains. PSA belongs to the kallikrein family and exerts serine protease activity.[2] Although its physiological actions are unknown, it is considered to play a role in the liquefaction of coagulated seminal fluid.

PSA protein is produced in prostatic epithelial cells in an androgen-dependent manner. Mediated by androgen receptors, androgen binds to the androgen response element located upstream of the PSA gene, and stimulates the production of the PSA messenger RNA and protein.

2. Prostate cancer and PSA

The expression of PSA protein is not specific to prostate cancer. It is specific to prostatic epithelial cells in various conditions including normal and hyperplasic conditions. However, while almost all PSA protein is secreted into seminal fluid in normal conditions, PSA protein leaks into blood in prostate cancer. Serum PSA measurement is, therefore, useful for the diagnosis and observation of prostate cancer. It is widely used as a blood marker for prostate cancer for the purposes of screening and detection of recurrence after treatment.[3]

Higher levels of serum PSA are associated with a higher probability of diagnosing prostate cancer. Prostate cancer is detected in 20–30% of cases showing PSA levels of 4.1–10 ng/m*l*, and 30–50% or more of cases showing PSA levels of 10 ng/m*l* or more. However, it should be noted that cancer is found in about 15% of patients showing normal PSA and induration of the prostate detected by digital rectal examination (DRE). Serum PSA increases with the progression of prostate cancer. Almost all cases of progressive prostate cancer with bone metastasis present abnormally elevated serum PSA.

3. Molecular forms of blood PSA and differences between assay kits

PSA in blood occurs in the form of free PSA and in forms bound to α1-antichymotrypsin and α2-macroglobulin (Fig. 1). Most PSA assay kits detect free PSA and α1-antichymotrypsin-bound PSA. It is desirable that a kit is capable of the simultaneous equimolar detection of both forms. However, different kits show different ability of equimolar detection.

Formerly, because of the differences in sensitivity and other properties of commercially available assay kits, there were wide variations in the results of PSA measurement depending on the type of kit used. Accordingly, the data were usually converted to results obtained with the Tandem-R kit, which was commonly used in Europe and the U.S.[4] However, this conversion was not always reliable because of the problem of equimolarity. Recent efforts toward standardization have greatly improved equimolarity among different kits, and interkit differences are diminishing.[5]

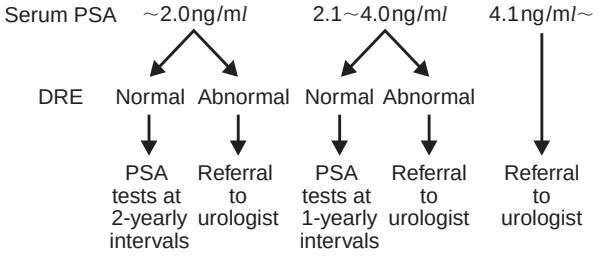

Fig. 2 Flow chart of prostate cancer diagnosis by serum PSA and digital rectal examination (DRE)

Significance of Serum PSA Measurement in Prostate Cancer Diagnosis

1. Evaluation of serum PSA and recommended action

A definite diagnosis of prostate cancer is made by histopathological diagnosis using needle core biopsy. Usually, indication for biopsy is determined based on serum PSA, digital rectal examination (DRE), and transrectal ultrasound findings. Of these 3 methods, serum PSA is the most effective in terms of sensitivity and specificity. Therefore, the need for referral to specialist urologists should be determined based on serum PSA and DRE findings (Fig. 2).

Specifically, all cases with PSA levels of 4.1 ng/m*l* or more should be referred to specialist urologists, as well as those showing PSA levels of 4.0 ng/m*l* or less and positive findings on DRE. The probability of patients with PSA levels below 2.0 ng/m*l* showing elevation to 4.1 ng/m*l* or more or developing cancer within 1 or 2 years is extremely low. Therefore, PSA measurement at 1-yearly intervals is recommended for cases showing PSA levels of 2.1–4.0 ng/m*l*, and PSA measurement at 2-yearly intervals is recommended for those showing PSA levels below 2.0 ng/m*l*.[6]

2. T1c prostate cancer

In the TNM classification proposed by the International Union Against Cancer (UICC) in 1992, T1c cancer was defined as a cancer detected by needle biopsy that was conducted because of elevated serum PSA despite the lack of abnormal findings on DRE, transrectal ultrasound, and MRI. The occurrence of T1c cancer is increasing rapidly with the widespread use of serum PSA measurement. In Japan, too, many cases of prostate cancer detected recently have been classified as T1c.

In T1c cancer, cancer is present despite the absence of clear induration or imaging abnormalities. In the diagnosis of such cancer, it is important to obtain biopsy specimens evenly from all parts of the prostate. For this reason, it has become common practice to diagnose T1c prostate cancer using random systematic prostate biopsies under transrectal ultrasound guidance.[7]

Factors Affecting Serum PSA

Diseases other than prostate cancer may cause elevation of serum PSA, and this fact needs attention in interpreting measurement data (Table 1).

1. Factors that can increase serum PSA

Slight increases in serum PSA may be observed in benign prostatic hyperplasia. Abnormally elevated levels of serum PSA may persist for a long time in acute prostatitis. Therefore, if prostatitis is suspected and elevated serum PSA is observed, remeasurement of serum PSA should be conducted after administering antibacterial drugs, and then the necessary action should be reconsidered. It should also be noted that a temporary increase in serum PSA may be caused by urinary retention, ejaculation, prostate palpation, urethral catheterization, prostate biopsy, and other kinds of stimulation.[1,2]

2. Factors that can decrease serum PSA

It is important to consider the possibility that administering antiandrogen may reduce serum PSA[8] and mask the presence of prostate cancer. When antiandrogen is prescribed as a

Table 1 Factors That Can Alter Serum PSA

Factors that can increase serum PSA
Benign prostatic hyperplasia, **Acute prostatitis**, Chronic prostatitis, **Urinary retention**, Ejaculation, Prolonged cycling, **Prostate biopsy**, **Urethral manipulation (Catheterization**, **Cystoscopy**, **etc.)**, Digital rectal examination
Factors that can decrease serum PSA
Hormone therapy for benign prostatic hyperplasia (Chlormadinone acetate, **Allylestrenol**, **etc.)**

Bold letters indicate factors causing particularly large alteration in serum PSA.

hormone therapy for benign prostatic hyperplasia, it must be preceded by serum PSA measurement and DRE to disprove the existence of cancer.

3. Variations in serum PSA

While serum PSA shows diurnal variations associated with variations in serum testosterone, the range of PSA variation is small. PSA is not excreted from the kidneys, and its half-life in blood is relatively long (2.2–3.2 days). Therefore, serum PSA in patients with renal insufficiency does not differ from that in healthy individuals, and no significant changes in serum PSA are observed between before and after hemodialysis.

Attempts to Improve Specificity

Cases showing serum PSA levels of 4.1–10 ng/m*l* are regarded as gray-zone cases, in which differentiation between prostate cancer and benign prostatic hyperplasia is an important clinical problem. Various attempts have been made to improve the accuracy of differential diagnosis of these diseases.

1. PSA density

The value obtained by dividing serum PSA level by prostate volume is called PSA density (PSAD; the ratio of PSA level to prostate volume). Taking advantage of the correlation between serum PSA and the size of adenoma in benign prostatic hyperplasia, this method intends to minimize the contribution of hyperplasia to PSA levles.[9] Several cut-off values have been proposed, e.g., 0.15 ng/m*l*/cc. This method is used as an aid in determining the necessity for prostate biopsy in gray-zone cases.

2. PSA free/total ratio

When we examine the percentages of different molecular forms of PSA in blood, it was found that the percentage of free PSA remains low in prostate cancer, as compared with that of α1-chymotrypsin-bound PSA. Based on this fact, attempts have been made to discriminate prostate cancer using the ratio of free PSA to total PSA measured in blood.[10] The cut-off level is usually set at 15–25%.

γ-seminoprotein (γ-Sm) is a blood marker for prostate cancer used in Japan. While γ-Sm has been identified to be the same substance as PSA, the measurement of γ-Sm mainly reflects the amount of free PSA. Based on this fact, the usefulness of the γ-Sm/PSA ratio has been reported.

3. PSA-ACT

As mentioned above, patients with prostate cancer show an elevated percentage of α1-antichymotrypsin-bound PSA (PSA-ACT). Attempts have been made to improve the accuracy of diagnosis by directly measuring PSA-ACT.

4. PSA velocity

Compared with non-cancer diseases, prostate cancer shows steady year-by-year increases in serum PSA. Based on this fact, it has been proposed that PSA velocity (PSAV; rate of change in PSA over time) calculated from successive measurements of serum PSA may be useful in discriminating cancer. The cut-off level is set at about 0.75 ng/m*l*/year.

5. Age-specific PSA reference ranges

Serum PSA increases gradually as the patient ages. Because of this fact, some researchers have recommended that the cut-off level for normal serum PSA should be defined according to age. An example of these age-specific reference ranges is: 2.5 ng/m*l* for the 40–49 age range, 3.5 ng/m*l* for the 50–59 age range, 4.5 ng/m*l* for the 60–69 age range, and 6.5 ng/m*l* for the 70–79 age range. However, in using this approach, attention must be paid to the existence of large ethnic differences.

As outlined above, a number of attempts have been made to improve the efficiency of diagnosis in gray-zone cases. However, no consensus has been reached as to the usefulness of these approaches and the appropriate cut-off levels.

Significance of Serum PSA Measurement in the Followup of Prostate Cancer

1. Serum PSA after radical prostatectomy

Because radical prostatectomy for prostate cancer removes all prostatic tissue including the normal parts, postoperative serum PSA levels are either zero or negligibly low. Almost all recurrent cases show increases in serum PSA some years before a clear manifestation of clinical recurrence. The elevation in serum PSA above the limit of measurement sensitivity is called "biochemical recurrence" or "PSA recurrence." Even earlier detection of the signs of recurrence has been attempted by measuring low levels of PSA with high-sensitivity PSA assay kits.

2. Serum PSA after radiotherapy for prostate cancer

Serum PSA also decreases in response to radiotherapy for prostate cancer. However, the decrease is slow and sometimes takes over one year to nadir. The PSA nadir level is not zero, but is usually in the range of 0.2–0.6 ng/m*l*. For this reason, determining "PSA recurrence" is based on the observation of three consecutive increases, rather than the absolute value of serum PSA.

3. Serum PSA after hormone therapy for prostate cancer

Serum PSA measurement is also useful in the followup after hormone therapy for prostate cancer. The PSA reactivity measured three or six months after treatment initiation is a significant predictor of long-term prognosis. Relapse of disease can be detected early based on "PSA relapse," which is defined as three consecutive increases in serum PSA.

Conclusion

Serum PSA measurement is an essential test in the diagnosis and treatment of prostate cancer. Because this test facilitates the simple screening for prostate cancer, its use is expected to become increasingly widespread in the future. It is hoped that physicians other than urologists also understand the characteristics and key points of this method, and use it actively in their practice.

REFERENCES

1) Stamey, T.A., Yang, N., Hay, A.R. *et al.*: Prostate-specific antigen as a serum maker for adenocarcinoma of the prostate. *N Engl J Med* 1987; 317: 909–916.
2) Rittenhouse, H.G., Finlay, J.A., Mikolajczyk, S.D. *et al.*: Human kallikrein 2 (hK2) and prostate-specific antigen (PSA): tow closely related, but distinct, kallikreins in the pros-

tate. *Clin Rev Clin Lab Sci* 1998; 35: 275–368.
3) Oesterling, J.E.: Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. *J Urol* 1991; 145: 907–923.
4) Kuriyama, M., Akimoto, S., Akaza, H. *et al.*: Comparison of various assay systems for prostate-specific antigen standardization. *Jpn J Clin Oncol* 1992; 22: 393–399.
5) Kano, S., Ishibashi, M. and Ito, Y.: Present state of diagnostic markers for prostate cancer. Present state of standardization of serum total PSA measurement — Results from "2000 survey" by the PSA ad hoc committee of the Japan Urological Association. *The Japanese Journal of Clinical Pathology* 2001; 49: 967–973. (in Japanese)
6) Carter, H.B., Epstein, J.I., Chan, D.W. *et al.*: Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer. *JAMA* 1997; 277: 1456–1460.
7) Suga, K., Akakura, K., Ueda, T. *et al.*: Association between clinical stage of prostate cancer and pathological findings of random systematic transperineal core biopsy under transrectal ultrasonography. *Int J Clin Oncol* 1999; 4: 353–357.
8) Montgomery, B.T., Young, C.Y., Bihartz, D.L. *et al.*: Hormonal regulation of prostate-specific antigen (PSA) glycoprotein in the human prostatic adenocarcinoma cell line, LNCaP. *Prostate* 1992; 21: 63–73.
9) Benson, M.C., Whang, I.S., Pantuck, A. *et al.*: Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. *J Urol* 1992; 147: 815–816.
10) Catalona, W.J., Partin, A.W., Slawin, K.M. *et al.*: Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. *JAMA* 1998; 279: 1542–1547.

Therapies for Prostate Cancer and Treatment Selection

JMAJ 47(12): 555–560, 2004

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Abstract: The number of patients with prostate cancer has been increasing rapidly as a result of the widespread use of prostate specific antigen (PSA) screening and the aging of society. In Japan, prostate cancer is now recording the highest rate of increase in prevalence amongst all types of cancer. Localized prostate cancer can be managed using various treatment options such as surgery, radiotherapy, and watchful waiting, and each of these therapies has further options. So long as patient selection is performed properly, the outcomes of these therapies are comparable. However, wide variations are seen in the effects of various therapies on complications and QOL. In addition, we must consider the fact that prostate cancer needs follow-up care for a relatively long period after treatment. Therefore, in choosing treatment options, we should consider not only the effects of treatment, such as survival, but also the changes in QOL after treatment. It is important to support patients through the provision of information concerning QOL, so that they can understand the treatment from a broader perspective.

Key words: Prostate cancer; Localized; PSA; QOL

Introduction

The number of patients with prostate cancer is increasing rapidly as a result of the widespread use of screening with prostate specific antigen (PSA), an effective tumor marker, and as a result of the aging of society. In the Japanese population, prostate cancer is now recording the highest rate of increase in prevalence among all types of cancer.

This article outlines the treatment options for prostate cancer, in particular early-stage cancer, showing a dramatic rate of increase in recent years.

Treatment Decision Processes with Patient Participation

Recent emphasis in the processes of cancer diagnosis and treatment has been placed on the

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importance of patient participation in treatment decisions, predicated on the provision of medical information covering all aspects of the disease. In the case of prostate cancer, we can use this approach as discussed below.

After a definite diagnosis is made based on biopsy, the patient is told he has cancer, and receives information on prostate cancer in general. He receives an explanation concerning the need for staging examinations and a rough plan for treatment. Nowadays, many patients obtain information via the Internet. In our hospital, we not only provide patients with a written explanation, but also recommend them to access the Japanese version (http://www.ccijapan.com) of Physician Data Query (PDQ®) maintained by the National Cancer Institute (NCI) in the U.S. to provide cancer information for patients.

Next, the patient receives comprehensive information on his condition, including clinical staging, malignancy (Gleason score), and PSA. A detailed explanation is given concerning treatment options and their benefits and risks. A nomogram for estimating pathological staging from the above clinical parameters has been developed and introduced in clinical practice.[1)]

The patient chooses the optimal treatment for himself, based on comprehensive consideration of the information. During this process, physicians should evaluate the medical appropriateness of the patient's choice and provide support toward treatment.

With these processes in mind, the following sections review therapies for early-stage prostate cancer and treatment selection.

Clinical Staging of Prostate Cancer

This section discusses important points regarding early-stage cancer as defined by clinical staging. Japanese Classification of Prostate Cancer and the TNM classification are illustrated. Conventionally, a cancer detected in the histopathological specimens from surgery for

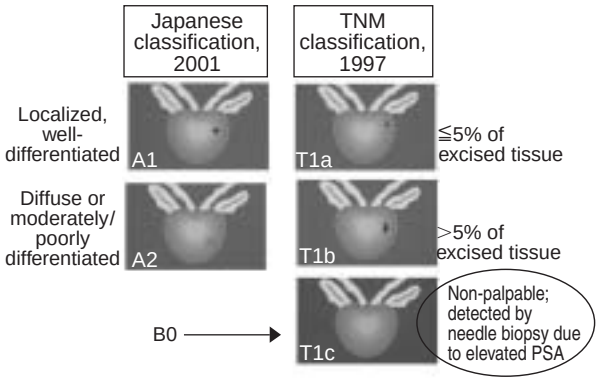

Fig. 1 Clinical staging of prostate cancer
(Detected incidentally by histopathological examination)

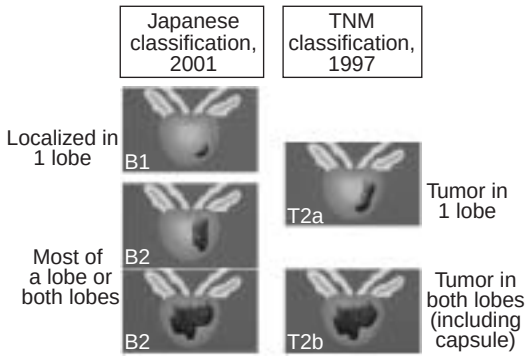

Fig. 2 Clinical staging of prostate cancer
(Palpable cancer localized in prostate)

prostatic hyperplasia is classified as stage A in the former and stage T1 in the latter. This classification is specific to prostate cancer (Fig. 1).

Recently, a rapidly increasing number of cancers that are non-palpable on digital rectal examination are detected by needle biopsy performed because of abnormally elevated PSA. These cancers are collectively classified as B0 or T1c. Currently, many of the cancers detected by PSA screening and subjected to curative treatment are classified as T1c, and these cancers represent a considerable part of all prostate cancer cases.[2)]

Palpable cancers localized within the prostate are classified as stage B or T2 (Fig. 2). Of these, many of the cases with palpable cancer in both lobes of the prostate (T2b) are considered

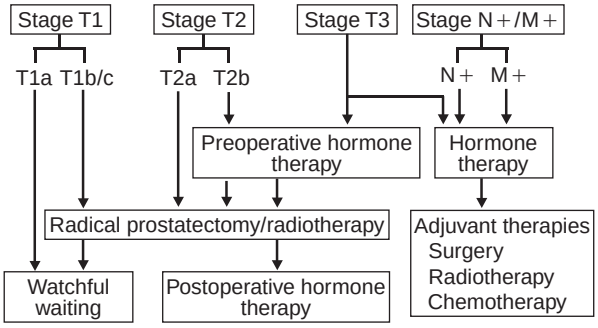

Fig. 3 Treatment strategies for prostate cancer by stage

Table 1 Treatment for Localized Prostate Cancer

- Radical prostatectomy
  - Retropubic approach, perineal approach, laparoscopic approach
- Radiotherapy
  - External irradiation
    - 3D conformal radiation, intensity modulated radiation therapy
  - Brachytherapy
- Hormone therapy
- Watchful waiting

to have histopathological extracapsular extension. If palpation or imaging diagnosis demonstrates extracapsular extension or seminal vesicle infiltration, the cancer is diagnosed as T3.

Treatment Strategies According to Staging

T1 and T2 cancers localized within the prostate are usually given curative treatment, such as radical prostatectomy and radiotherapy (Fig. 3). In locally advanced T3 cancer, the effectiveness of surgery or radiotherapy alone is limited, and a combination with hormone therapy is selected in many cases.

Cases with metastasis are treated with hormone therapy using LH-RH agonists, antiandrogens, or castration. However, hormone therapy is palliative. After a period of response, many cases develop into a condition of hormone-resistant cancer. Few chemotherapy regimens are effective for prostate cancer. While some are effective, none has been reported to contribute to the elongation of survival.

Minute T1 cancers are classified as T1a, and most of these do not require treatment. Nonpalpable cancers that are detected only by abnormal PSA levels, i.e., T1c cancers, include a wide spectrum of conditions from non-life-threatening minute cancer to locally advanced cancer. The treatment for T1c cancers, therefore, has many options, and it is important for us to understand characteristics of each treatment. If the disease is well-differentiated minute cancer in elderly patients, watchful waiting can be a good option for T1c cancer. Other cases are treated with curative therapies such as surgery and radiotherapy.

Treatment for Localized Prostate Cancer

The main treatment options are radical prostatectomy, radiotherapy, and watchful waiting (Table 1). Hormone therapy is not a curative therapy; it should always be considered as a palliative treatment. Hormone therapy is often selected for exacerbation after watchful waiting and recurrence after curative treatment.

As mentioned above, watchful waiting is an important treatment option for suspected well-differentiated minute cancer and for elderly patients. In this case, regular PSA tests are essential. It may be said that watchful waiting is a viable treatment option owing to the ability of simple PSA tests to predict disease progression.

The recent progress of radiotherapy has also been remarkable. As for external irradiation, conventional rotation therapy and pendulum irradiation are being replaced by new methods, such as 3-D conformal radiation and intensity modulated radiation therapy (IMRT). In these methods, careful preplanning of the field of irradiation to fit the shape of the prostate enables high-dose irradiation to the organ

with the primary cancer while minimizing the dose to surrounding organs. These methods achieved an enhancement of anticancer efficacy and a marked reduction of bladder and rectal disturbances.

Brachytherapy, which uses small radioactive sources placed in the prostate, is gaining support recently. This treatment is being performed as frequently as surgery in the U.S. Brachytherapy was approved in Japan in 2003, and its use as a low-invasive treatment is expected to expand.

As for surgery, radical prostatectomy is the most widely used treatment for early-stage prostate cancer.[3] Operation methods have improved greatly in the last 10 years, and very stable outcomes are reported nowadays. In view of the invasiveness of treatment and its contribution to survival, patients considered for surgery should have at least 10 years of life expectancy.

Types of Surgical Therapy

A number of methods have been developed for radical prostatectomy, and each has various advantages.

The retropubic approach is the one used most frequently, and this method is well established. The perineal approach, as the name implies, does not involve surgical operation on the lower abdomen, and thus is less surgically invasive. The use of this method is also slowly increasing in Japan.

Laparoscopic radical prostatectomy is a newly developed method in which all procedures are performed using video assistance. Its advantages are small surgical wounds and quick postoperative recovery. However, much is left for future evaluation with respect to complete cancer elimination and functional recovery. Because laparoscopic radical prostatectomy has not been covered by national health insurance, patients who desire this surgery must bear the cost of treatment.

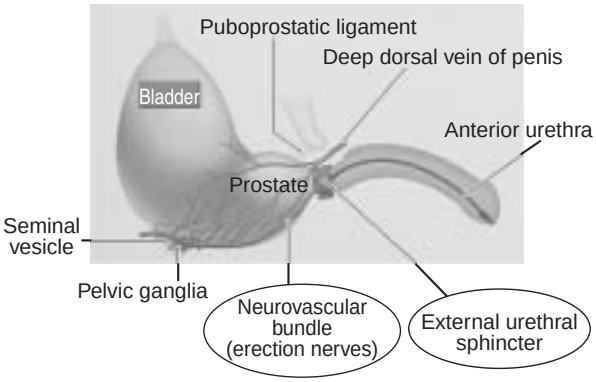

Fig. 4 Anatomy around the prostate (lateral view)
(Tobisu, K.: *Cancer Surgery — Surgical Techniques Series, Urinary Cancers* (Kakizoe, T. ed.). Medical View Co., Ltd., Tokyo, 1992; pp. 66)

Anatomical Features of the Prostate and Treatment Complications

In discussing the characteristics of curative therapies for prostate cancer, it is important to understand the anatomy of the prostate and surrounding structures (Fig. 4). During surgery, the prostate and the seminal vesicle are removed as a mass, and the bladder is anastomosed to the urethra. The apical portion of the prostate is in contact with the external urethral sphincter. Along the posterior and lateral aspects of the prostate run the rectum and the cavernous nerves of the penis, the so-called "erection nerves."

As seen from the anatomic locations of these structures, curative therapies for prostate cancer must be viewed from 2 aspects: (1) complete resection or disappearance of the prostate and (2) preservation of the important function of surrounding structures. With the increasing knowledge of pelvic anatomy, treatment techniques have been improved, and surgery that spares the erection nerves is extensively performed. The advance in preservation of function has been remarkable.

On the other hand, prostate cancer often develops in the posterior-lateral aspect of the prostate, i.e., in the vicinity of the erection nerves. Because the complete cure of cancer is

Table 2 Therapies for Localized Prostate Cancer and Complications

• Curative radical prostatectomy Urinary incontinence, sexual dysfunction (ED), stenosis of vesicourethral anastomosis, general complications of surgery
• Radiotherapy Anorectal injury, bladder dysfunction, late radiation injury
• Watchful waiting Psychological stress, stage progression

Table 3 Therapies for Early-Stage Prostate Cancer and QOL

General health related QOL	Surgery≒Radiotherapy
Disease-specific QOL:	
Urinary continence	Surgery＜Radiotherapy
Lower urinary tract symptoms	Surgery＞Radiotherapy
Sexual function	Surgery＜Radiotherapy
Bowel function	Surgery＞Radiotherapy

Good＞Poor

the priority in surgery, the appropriateness of nerve-sparing surgery must be determined carefully based on information such as preoperative tumor localization.

For these anatomical reasons, each type of therapy for localized prostate cancer may cause characteristic complications (Table 2).

Curative radical prostatectomy has been reported to cause postoperative urinary incontinence, sexual dysfunction (erectile dysfunction; ED), stenosis of vesicourethral anastomosis, and other specific complications, in addition to wound infection and other general surgery complications. Thanks to the improvement in methods of operation, urinary incontinence is rarely severe and disabling. It usually occurs transiently after surgery, and improves with the passage of time.

Postoperative ED is inevitable when nerves are not preserved. With nerve-sparing surgery, functional recovery can be expected to some extent. Recovery of sexual function can be expected even with unilateral nerve sparing procedures. When recovery of erection is insufficient, the use of Viagra® is likely to achieve recovery of sexual function in more than half of all cases.[4)]

Complications of radiotherapy typically include anorectal injury (diarrhea, bloody stools, anal pain) and bladder dysfunction (increased urinary frequency, miction pain, difficulty in urinating) resulting from radiation exposure of adjacent organs. Many cases improve gradually with the passage of time after treatment. As a peculiarity of radiotherapy, rectal injury or ED can develop late after treatment. Recent development of 3-D conformal radiation and intensity modulated radiation therapy has reduced the occurrence of these complications.

In contrast with the above 2 types of curative therapies, watchful waiting cannot cause any direct complications. On the other hand, prolonged observation without treatment may cause a certain amount of psychological stress to the patient and a risk for stage progression during observation.

Therapies for Early-Stage Prostate Cancer and QOL

Based on the points discussed above, we compare the patient's QOL after surgery and radiotherapy in the treatment for early-stage prostate cancer (Table 3).

No difference is reported to occur between the effects of surgery and radiotherapy on general health-related QOL, including physical function, mental health, social life, and daily role function.

On the other hand, there are marked differences in disease-specific QOL directly related to prostate cancer treatment.[5)] With respect to urinary continence, radiotherapy provides better QOL outcomes than surgery. However, because surgery removes the prostate with hyperplasia, it dramatically improves lower urinary tract symptoms such as difficulty in

urinating and increased urinary frequency. Radiotherapy often causes transient aggravation of urination symptoms shortly after treatment, as a result of inflammation and other effects of irradiation. With respect to sexual function, surgery tends to result in poorer QOL because of the risk for surgical damage to erection nerves. Since surgery has almost no effect on the rectum, it provides better QOL related to bowel function than radiotherapy.

As summarized above, the 2 representative methods of curative treatment provide characteristic QOL outcomes after treatment. It is important that patients understand these differences. We also need to pay attention to the fact that this scheme on QOL may change with progress after treatment. Finally, it should be noted that recent remarkable developments in both surgery and radiotherapy have been reducing these differences in QOL outcome.

Conclusion

This paper outlines the therapies for prostate cancer and the process of treatment selection focusing particularly on localized prostate cancer, which is often detected by PSA tests. The treatment for localized prostate cancer has many options, including surgery, radiotherapy, and watchful waiting, and each of these therapies also includes many options. As long as patient selection is performed properly, the outcomes of these therapies are comparable. Wide variations are seen in the effects of various therapies on complications and QOL. In addition, we must consider the fact that prostate cancer needs followup care for a relatively long period after treatment.

Therefore, in choosing treatment options, we should consider not only treatment effects such as survival but also the changes in QOL after treatment. It is important to support patients through the provision of information concerning QOL, so that they can understand the treatment from a broader perspective.

REFERENCES

1) Partin, A.W., Mangold, L.A., Lamm, D.M. *et al.*: Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. *Urology* 2001; 58: 843–848.
2) Non-palpable (T1c) prostate cancer — a new approach. Arai, Y. (planning & organization), Yoshida, O. (ed.), Urology View 1 (2), Medical View Co., Ltd., 2003. (in Japanese)
3) Arai, Y., Egawa, S., Tobisu, K. *et al.*: Radical retropubic prostatectomy: Time trends, morbidity and mortality in Japan. *BJU Int* 2000; 85: 287–294.
4) Arai, Y., Nakagawa, H. and Namiki, S.: ED and surgery for pelvic malignant tumors. *The Journal of Therapy* 2003; 84 (11): 135–139. (in Japanese)
5) Namiki, S., Tochigi, T., Arai, Y. *et al.*: Health related quality of life after radical prostatectomy in Japanese men with localized prostate cancer *Int J Urol* 2003; 10: 643–650.

Diagnosis and Treatment of Prostatitis

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Abstract: Among various prostatic diseases, those presenting diverse symptoms including increased urinary frequency, feeling of incomplete emptying, difficulty in urination, perineal pain or discomfort, low back pain, and lower abdominal pain are categorized as prostatitis syndrome. Prostatitis syndrome is broadly divided into acute bacterial infection and chronic prostatitis, and the latter includes various forms of disease ranging from those involving bacterial infection to those accompanying no inflammatory reaction. Each of the disease groups classified in chronic prostatitis has been poorly understood with respect to etiology, pathology, diagnosis, and treatment. To tackle these diseases, new attempts are being made, including new classification, scoring of symptoms and their severity, the application of molecular biological techniques for diagnosis, and the development of treatment methods. Future developments are expected to lead to the elucidation of the etiology of chronic prostatitis through the accumulation of data, as well as the establishment of new evidence-based methods for diagnosis and treatment.

Key words: Acute bacterial prostatitis; Chronic bacterial prostatitis; Non-bacterial prostatitis; Prostatodynia

Introduction

Among the independent prostatic diseases that do not have any underlying disease in the genitourinary system, a group of disorders presenting diverse symptoms including increased urinary frequency, feeling of incomplete emptying, difficulty in urination, perineal pain or discomfort, low back pain, and lower abdominal pain are categorized as prostatitis syndrome.

Drach *et al.*[1] classify prostatitis syndrome into acute bacterial prostatitis, chronic bacterial prostatitis, non-bacterial prostatitis, and prostatodynia (Table 1).

In 1995, the National Institute of Health (NIH) in the U.S. proposed a new disease classification[2] (Table 1). The NIH classification defines acute bacterial prostatitis as type I and chronic bacterial prostatitis as type II, while non-bacterial prostatitis and prostatodynia are combined in type III, chronic abacterial prostatitis or chronic pelvic pain syndrome. Type III

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Table 1 Classification of Prostatitis Syndrome

Classification by Drach *et al.*[1]	NIH classification[2]
Acute bacterial prostatitis	Type I : Acute bacterial prostatitis
Chronic bacterial prostatitis	Type II : Chronic bacterial prostatitis
Non-bacterial prostatitis Prostatodynia	Type III: Chronic abacterial prostatitis (Chronic pelvic pain syndrome) A: Inflammatory B: Noninflammatory
	Type IV: Asymptomatic inflammatory prostatitis

was further subdivided into inflammatory (type IIIA) and noninflammatory (type IIIB). The NIH classification created a new category of asymptomatic inflammatory prostatitis (type IV) to include cases lacking clinical symptoms and showing histopathological findings of inflammation or the presence of leukocytes in prostatic secretion tested for other diseases.

Usually, the term "acute prostatitis" refers to acute bacterial prostatitis, i.e., NIH type I, and the term "chronic prostatitis" refers to a group of diseases including chronic bacterial prostatitis, non-bacterial prostatitis, and prostatodynia, which correspond to NIH type II, type IIIA, and type IIIB, respectively. Even with this new classification, the etiology and pathology of diseases constituting chronic prostatitis have not been fully elucidated, and clinical severity determination and systematic treatment methods have not yet been established.

Under these circumstances, the NIH published the NIH Chronic Prostatitis Symptom Index.[3] This index, designed to evaluate pain, discomfort, urination symptoms, and the effects of symptoms on daily life in scores, is expected to be used to determine severity and evaluate various treatment methods. A Japanese version of this index has been developed, and studies to examine its validity and usefulness have commenced. However, data based on these new approaches have not been accumulated sufficiently so far. This article outlines the clinical characteristics and treatment of various diseases in prostatitis syndrome according to conventional classification.

Acute Prostatitis

Acute bacterial prostatitis with rapid onset and development corresponds to type I in the NIH classification. This disease is caused by retrograde infection of bacteria from the urinary tract into the prostate. It starts abruptly with fever accompanying chills and shivering and bladder irritation symptoms, such as increased urinary frequency and miction pain, and eventually causes ejaculation pain, urinary disturbance, and sometimes urinary retention. Digital rectal examination reveals a swollen soft prostate presenting heat sensation and tenderness. Urine tests show pyuria and bacteriuria. Prostate massage is contraindicated during the acute phase because of the risk of inducing sepsis. First-voided urine or midstream urine is submitted to bacterial culture test for identification of causative bacteria.

Most of the bacteria causing acute bacterial prostatitis are Gram-negative bacilli, including *Escherichia coli* responsible for 60% of cases. Antibacterial chemotherapy with second and third generation cephems and carbapenems, which have potent antibacterial activity against *E. coli* and other potential causative bacteria, is effective, although penetration into the prostate is not always beneficial. New oral quinolones are considered useful in treating acute bacterial prostatitis because they have wide antibacterial spectra covering almost all caus-

Table 2 Diagnosis of Prostatitis Syndrome

Classification by Drach *et al.*[1]	NIH classification[2]	Expressed prostatic secretion or VB3[4,5]	
		Leukocytes	Bacteria
Acute bacterial prostatitis*	Type I *	+	+
Chronic bacterial prostatitis	Type II	+	+
Non-bacterial prostatitis	Type IIIA	+	−
Prostatodynia	Type IIIB	−	−

*Because prostate massage is contraindicated, diagnosis of acute prostatitis is made based on the results of urine tests and bacterial culture tests on first voided urine or midstream urine, combined with the palpitation findings of a swollen prostate with heat sensation and tenderness.

ative bacteria and exert potent antibacterial activity.

The selection and switching of antibacterial agents are made based on the drug sensitivity of causative bacteria indicated by the bacteriological tests of urine. Generally, severe cases are first treated with a parenteral cephem or carbapenem, and switched to oral fluoroquinolones after the resolution of acute symptoms. Treatment for acute bacterial prostatitis should basically be in-patient care with infusion and intravenous antibacterial agents although mild cases may be treated on an outpatient basis using oral fluoroquinolones. The use of antibacterial agents should be continued for 4 to 6 weeks.

Chronic Prostatitis

Chronic prostatitis with gradual clinical progression is a group of conditions including chronic bacterial prostatitis, non-bacterial prostatitis, and prostatodynia. The diagnosis of each condition is made based on leukocyte counts and bacterial culture results in the urine and expressed prostatic secretion (EPS) collected by the Meares and Stamey method[4] (Fig. 1) (Table 2).

In this sampling method, 10 m*l* of first voided urine is taken as VB1, and midstream urine after voiding 200 m*l* is taken as VB2. Prostatic massage is performed thereafter, and expressed prostatic secretion is collected. The patient is instructed to void again after massage, and 10 m*l* of first-voided urine is taken as VB3.

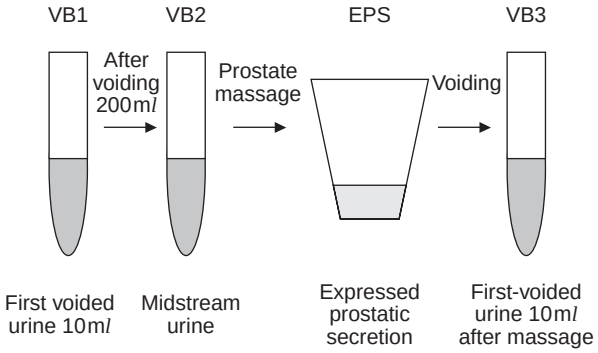

Fig. 1 Meares and stamey method
(Meares, E.M. and Stamey, T.A.: *Invest Urol* 1968; 5: 492–518)

However, because the sampling using the Meares and Stamey method is tedious and impractical in the clinical setting, a pre- and post-massage test using the urine taken before and after prostate massage has been proposed.[5] In this method, midstream urine before prostate massage and 10 m*l* of first-voided urine after massage are collected. The post-massage urine corresponds to VB3 in the Meares and Stamey method.

Whichever sampling method is used, urine samples are subjected to quantitative bacterial culture tests and microscopic examination of urinary sediment. EPS is also subjected to culture tests and microscopy.

1. Chronic bacterial prostatitis

Chronic bacterial prostatitis corresponds to type II in the NIH classification. According to the UTI Efficacy Evaluation Criteria in Japan,[6] diagnosis as having this disease is made when microscopic examination of EPS or VB3 urinary sediment shows an increased leukocyte count of 10 or more per field, and bacterial culture results in the isolation of at least 10^3 CFU/m*l* Gram-negative bacilli or 10^4 CFU/m*l* Gram-positive cocci. The most frequently isolated bacteria are *E. coli* among Gram-negative bacilli and *Enterococcus* and *Staphylococcus* species among Gram-negative cocci. However, bacteria are isolated only at a frequency of 5 to 10% from patients with diseases showing symptoms of chronic prostatitis. Digital rectal examination of the prostate does not show characteristic findings in most cases although it may reveal mild tenderness.

Fluoroquinolones are the first choice of antibacterial agents for chronic bacterial prostatitis because of their wide antibacterial spectrum, good penetration into prostatic tissues, and suitability for outpatient treatment. An antibacterial agent is administered first for 4 weeks. If a response is obtained, the regimen is continued for an additional 4 weeks. If no response is seen, the regimen is changed based on the type and drug resistance of bacteria cultured from VB3 or EPS. Because treatment usually requires a long time, the development of any side effects must be monitored carefully.

2. Non-bacterial prostatitis

In the NIH classification, non-bacterial prostatitis is classified as inflammatory type-IIIA disease in the category of chronic abacterial prostatitis without proof of infection. Diagnosis of this disease is made when the presence of inflammation is suggested by an increased leukocyte count of 10 or more per field in microscopic examination of EPS or VB3 urinary sediment, but when bacterial culture does not detect inflammation-causing bacteria.

The presumed causes of this disease include chlamydia, mycoplasma, ureaplasma, and other bacteria that do not grow in general bacterial cultures, as well as an inflammation reaction due to the intraprostatic reflux of urine, but the pathology of this disease has not been clarified. However, recent examination of bacterial genes in prostatic tissues using molecular biological methods for bacteria detection suggests that this disease may involve some forms of bacterial infection.[7]

For this reason, antibacterial chemotherapy is attempted in treatment for non-bacterial prostatitis, similarly to treatment for chronic bacterial prostatitis. Fluoroquinolones are preferred as they have wide antibacterial spectra; exert antibacterial activity against chlamydia, mycoplasma, and ureaplasma, and show good penetration into prostatic tissues. Considering the possible involvement of chlamydia and other bacteria, the use of tetracyclines that are effective against these bacteria may also be an option.

An antibacterial agent is administered first for 4 weeks. If a response is obtained, the regimen is continued for additional 4 weeks. If the patient complains of difficulty in urination, the regimen is combined with an α1-blocker as used for prostatic hyperplasia or an anti-inflammatory plant extract. If he has symptoms of an unstable bladder, such as increased urinary frequency and urgency, anticholinergic drugs and smooth muscle relaxants are added to the regimen. In refractory cases, treatment for prostatodynia as discussed in the next section is incorporated.

3. Prostatodynia

In the NIH classification, prostatodynia corresponds to noninflammatory type-IIIB disease in the category of chronic abacterial prostatitis. Diagnosis of this disease is made when no leukocytes are observed on microscopic examination of EPS or VB3 urinary sediment, and no signs of inflammation are recognized.

Similarly to non-bacterial prostatitis, the etiology of this disease is unknown. Presumed

causes include psychogenic factors, pelvic vein congestion, and hypertonic pelvic floor muscles. When the involvement of psychogenic factors is strongly suspected, the use of minor tranquilizers and counseling are effective in some cases.

When the involvement of pelvic vein congestion is suspected because MRI or transrectal ultrasound tomography indicates the dilation of veins on the anterior surface of the prostate, in particular Santorini's plexus, and when the condition is accompanied by hemorrhoids, such patients may benefit from a Chinese herbal medicine for resolving blood congestion ("oketsu"), such as keishi-bukuryo-gan (Cinnamon & Hoelen Formula). When hypertonicity of pelvic floor muscles is strong, low-frequency electrical acupuncture and moxibustion are attempted. In addition, thermotherapy as used for prostatic hyperplasia has been reported to be effective in non-bacterial prostatitis and prostatodynia.

The symptoms of chronic prostatitis often repeat improvements and exacerbations, and they resist treatment in many cases. Factors leading to the exacerbation of symptoms include drinking, driving, prolonged sitting for deskwork, fatigue, stress, and coldness. Some patients who feel discomfort or mild pain during ejaculation refrain from ejaculation for fear that ejaculation might aggravate the symptoms. However, ejaculation actually improves symptoms in many cases.

In view of the present situation in which treatment for chronic prostatitis has not been established, it is important for us to instruct patients to avoid or curtail factors that aggravate symptoms in daily life, as well as to encourage practices that ameliorate symptoms.

Conclusion

Among various disease groups categorized in prostatitis syndrome, those classified in chronic prostatitis have been poorly understood with respect to etiology, pathology, diagnosis, and treatment. To tackle these diseases, new attempts are being made, including new classification, scoring of symptoms and their severity, the application of molecular biological techniques for diagnosis, and the development of treatment methods.

Future developments are expected to lead to the elucidation of the etiology of chronic prostatitis through the accumulation of data, as well as the establishment of new evidence-based methods for diagnosis and treatment.

REFERENCES

1) Drach, G.W., Fair, W.R., Meares, E.M. *et al.*: Classification of benign diseases associated with prostatic pain: prostatitis or prostatodynia? *J Urol* 1978; 120: 266.
2) Executive summary: NIH workshop on chronic prostatitis. Bethesda, Maryland, 1995.
3) Litwin, M.S., McNaughton-Collins, M., Fowler, F.J. Jr. *et al.*: The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. *J Urol* 1999; 162: 369–375.
4) Meares, E.M. and Stamey, T.A.: Bacteriologic localization patterns in bacterial prostatitis and urethritis. *Invest Urol* 1968; 5: 492–518.
5) Nickel, J.C.: The Pre and Post Massage Test (PPMT): a simple screen for prostatitis. *Tech Urol* 1997; 3: 38–43.
6) UTI Efficacy Evaluation Criteria (3rd. Ed.) Appendix. *Chemotherapy* 1991; 39: 894–933.
7) Krieger, J.N., Riley, D.E., Roberts, M.C. *et al.*: Prokaryotic DNA sequences in patients with chronic idiopathic prostatitis. *J Clin Microbiol* 1996; 34: 3120–3128.

New Topics in Aspirin Therapy

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Abstract: Aspirin (acetylsalicylic acid, ASA), which was initially developed as an analgesic anti-inflammatory agent, has come to be the basis of antiplatelet therapy, and firm evidence supporting its usefulness has continued to accumulate. ASA irreversibly inhibits platelet function by acetylating cyclooxygenase (COX), which is involved in the production of a potent platelet stimulator, thromboxane A_2. There are two types of COX, one that is constitutively expressed in platelets (COX-1) and another that is induced in other tissues, including vascular endothelial cells (COX-2). Although ASA inhibits COX-1 more selectively, it also exerts an inhibitory effect on COX-2, the mechanism of which is considered partly a result of salicylation. The inhibition of COX-2 by ASA forms the basis of its anticipated role in the prevention of colorectal cancer and Alzheimer's disease and the inhibition of the progression of these diseases. It has been pointed out that the incidence of cardiovascular events tends to be high among patients who are not responsive to ASA (aspirin-resistant patients), but the reason for this increased incidence remains unclear. Interesting discussion in regard to ASA is likely to emerge in the future.

Key words: Aspirin; COX-1; NSAID; Antiplatelet therapy

Introduction

Aspirin, or acetylsalicylic acid, is a long-established drug with a history of more than 100 years since its synthesis in 1899 by Hoffman of Bayer Co., Ltd., of Germany. Aspirin, an over-the-counter drug that can be taken easily, was produced by enhancing the efficacy of salicylic acid, an active component of herbal medicines, including willow leaves. These herbs have been known to have analgesic properties since the days of Hippocrates. Although aspirin is the trade name of the acetylsalicylic acid manufactured by Bayer, it is now commonly used as a generic term, even in the scientific literature.

Although aspirin was used as an analgesic anti-inflammatory agent for five decades, in the 1960s it gradually became apparent that an adverse effect, namely, bleeding, is a by-

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product of its inhibitory effect on platelet aggregation. At about the same time, through rapidly progressing studies on prostaglandins, it became apparent that aspirin inhibits biosynthesis of the prostaglandin system, particularly that of thromboxane A_2 (TXA_2), a potent platelet agonist. This is the mechanism of aspirin's antiplatelet effect. In fact, it had long been noted that ischemic vascular disorders such as myocardial infarction and cerebral infarction were less frequent among regular aspirin users. As evidence accumulated, aspirin became recognized as an anti-thrombotic agent, rather than solely an anti-inflammatory drug.

In 1979, the US Food and Drug Administration (FDA) approved aspirin as a preventive therapy for recurrent stroke, and its indications were extended to the prevention of recurrent myocardial infarction in 1985. Thereafter, clinical data continued to accumulate, and statistical data from a study by an international study group, the Antiplatelet Trialists' Collaboration (APT) study, were published in 1994, helping to establish antiplatelet therapy including aspirin as a first-line measure for the treatment and prevention of recurrence of arterial thrombosis.[1)] Japan, which was slower to follow this trend, approved the use of aspirin for antiplatelet therapy in 2000.

This paper outlines recent topics on the efficacy of aspirin from the clinical viewpoint, while tracing the basic characteristics of the drug.

Pharmacology of Aspirin

When platelets are activated at the site of thrombus formation, arachidonic acid is cleaved from membrane phospholipids as the intracellular calcium concentration increases. This fatty acid then is converted to the very unstable prostaglandin G_2/H_2 by the action of cyclooxygenase (COX). TXA_2 then is produced by thromboxane synthetase, which is specific to platelets. TXA_2 has a potent platelet-activating effect, and induces stability of platelet aggregates by promoting further activation of platelets themselves. Aspirin inhibits the function of COX, the rate-limiting enzyme for this pathway, and thereby inhibits the stabilization of platelet aggregates and formation of platelet thrombi.

Aspirin exerts its action by causing acetylation of the enzyme with the acetyl group of its molecule at the 529th amino acid serine, which lies in the vicinity of the active center of the enzyme's configuration. The important point is that this change is irreversible. Platelets are cells devoid of nuclei. Once its function has been irreversibly suppressed by aspirin, the enzyme in the cell exists as it is without replacement by a new enzyme until the life of the cell ends. In other words, the pharmacologic effect of aspirin lasts for more than a week, the life span of a platelet.

1. COX-1 and COX-2

COX, the target of aspirin, is present in all tissues. In vascular endothelial cells, for example, it induces the production of prostacyclin (or prostaglandin I_2), the physiological action of which is opposed to TXA_2, i.e., it has an antiplatelet action. Therefore, a problem theoretically can arise here. Aspirin also inhibits prostacyclin, which has an antiplatelet action, and the possibility exists that the antiplatelet effect resulting from the inhibition of TXA_2 production is attenuated or eliminated. This is the so-called aspirin dilemma.

Fortunately, unlike the platelet, continuous protein synthesis in endothelial cells renews the nonacetylated enzyme. In addition, the cyclooxygenase present in platelets (COX-1) is more sensitive to aspirin than that present in endothelial cells (COX-2). Therefore, it is possible to overcome this problem by lowering the dose of aspirin. This is the basis of low-dose aspirin in anti-thrombotic therapy.[2)] Since aspirin inhibits the production of prostaglandin E_2, which plays an important role in maintaining the homeostasis of gastric mucosal cells, it is speculated that the use of aspirin may be asso-

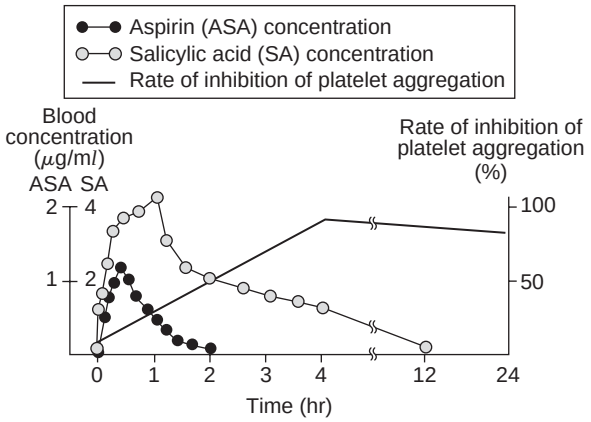


Fig. 1 Pharmacologic effects and blood concentrations of drug after a single aspirin dose of 80 mg (Adapted to a diagram from data reported in reference 4.)

Aspirin is absorbed from the intestinal tract and converted to salicylic acid by rapid deacetylation with esterase in the liver. Aspirin reaches its peak blood concentration at about 15 minutes, and is then eliminated from the systemic circulation in 2 hours. In contrast, salicylic acid is present in the blood for up to 12 hours or more. The inhibitory effect on platelet aggregation reaches its maximum level 4 hours after aspirin administration, and decreases gradually thereafter at a rate of about 10% per day in proportion to the life span of platelets. It is preferable to increase the dose if an acute antiplatelet effect is desired.

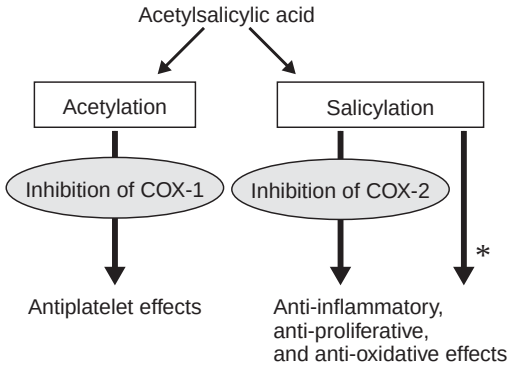


Fig. 2 Pharmacologic effects of aspirin

Aspirin (acetylsalicylic acid) exerts its pharmacologic effects by acetylation and salicylation of the target molecule. Antiplatelet effects are achieved by selective acetylation of COX-1, and anti-inflammatory, anti-proliferative, and anti-oxidative effects are achieved by salicylation of COX-2 and various signal enzymes (*) related to inflammation and cell proliferation.

ciated with adverse reactions such as gastrointestinal symptoms and gastric ulcer.

In addition to aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) also exert anti-inflammatory actions by similarly inhibiting COX. However, their actions are reversible, unlike those of aspirin, although NSAIDs are more potent than aspirin. The antiplatelet effects of NSAIDs attenuate as their blood concentrations decrease.

In recent years, it has become apparent that there are two COX isozymes with different types of gene regulation: COX-1, which is distributed widely and constantly over platelets and gastric mucosal cells, and COX-2, which is induced in cells through stimulation by inflammatory cytokines and growth factor.[3] Therefore, the chronic inflammatory reaction depends on COX-2. Characteristically, the affinity of NSAIDs, including aspirin, for these two COX isozymes varies among different drugs. While many NSAIDs are capable of inhibiting both isozymes to some extent, the inhibitory action of aspirin is more specific to COX-1. Anti-inflammatory drugs selectively acting on COX-2 have recently become available for practical use. As characteristic features, these drugs are associated with hardly any gastrointestinal problems resulting from the inhibition of COX-1 or bleeding symptoms induced by antiplatelet effects.

2. Acetylation and salicylation

After its absorption from the intestinal tract, aspirin rapidly inactivates COX-1 in platelets by acetylation during the enterohepatic circulation of the drug, and is immediately deacetylated into salicylic acid by esterase in the liver. Aspirin is eliminated from the systemic circulation following its peak concentration, which is achieved only about 15 minutes after its administration. However, the salicylic acid converted from aspirin can remain in blood for more than 12 hours depending on its dose (Fig. 1).[4] As mentioned earlier, salicylic acid has long been known as an anti-inflammatory drug. It has been unclear as to whether the antithrombotic effects of aspirin can be explained solely by its antiplatelet effects via acetylation.

In actuality, a number of basic experiments have suggested the possibility that the action of the metabolite salicylic acid is also involved (Fig. 2).[5)]

More specifically, it has become apparent that salicylic acid may exert anti-proliferative and anti-inflammatory actions in a dose-dependent manner by inhibiting the proliferation of smooth muscle cells constituting the vascular wall and by inhibiting the inflammation-stimulated increase in the adhesiveness of macrophages. The targets are considered to be the key transcription factors NFκB and AP1 and various enzymes in the Ras/MAP kinase system and the PI3 kinase system, which are major signal transmission pathways for inducing these cell responses.

It has previously been noted that salicylic acid may selectively inhibit COX-2. The current view of the pathogenesis of arterial thrombosis is that arterial thrombosis originates from atherosclerosis, the basis being chronic inflammation of the vascular wall. Therefore, it is possible that salicylation by aspirin, or acetylsalicylic acid, exerts a protective effect against the progression of atherosclerotic lesions. To achieve this protection, it may be necessary to obtain higher blood concentrations of salicylic acid by increasing the dose of aspirin, as in cases of anti-rheumatic therapy. On the other hand, dose increase is far from acceptable as an anti-thrombotic medication in view of the aspirin dilemma, and it is obvious that it would be associated with a higher incidence of side effects such as gastrointestinal disorders.

3. Inhibitory action of NSAIDs on the effects of aspirin

Aspirin has very high selectivity for COX-1. Among other NSAIDs, COX-1/COX-2 selectivity varies according to the drug. Importantly, some of these NSAIDs have a COX-1 inhibitory action that is antagonistic to that of aspirin. For the substrate arachidonic acid to undergo enzymatic processing, it is necessary that it reach the active center of COX-1, which is located deep inside the hydrophobic pocket, which has a narrow entrance. Aspirin and other NSAIDs inhibit access of the substrate by, respectively, acetylating the 529th amino acid, i.e., a serine residue lying near the active center, and by directly binding to the active center. Therefore, if an NSAID, which is a macromolecule, binds to COX-1 in advance, no effects can be expected from aspirin.[3)]

When an 81 mg dose of aspirin and 400 mg dose of highly COX-1-selective ibuprofen were administered at a 2-hour interval in the morning on 6 consecutive days, the order of the two doses was critical. When ibuprofen was administered prior to aspirin, only the reversible inhibition of COX-1 was noted, whereas the stable antiplatelet effects of aspirin occurred when the two drugs were administered in the reverse order.[6)] In addition, when continuous use of enteric-coated aspirin was combined with ibuprofen, 3 times a day, the stable antiplatelet effects of aspirin were suppressed. On the other hand, no such aspirin antagonism as observed with ibuprofen occurred when a selective COX-2 inhibitor, rofecoxib, and diclofenac or acetaminophen, which have high selectivity for COX-2, were used. It is also known that indomethacin acts similarly to ibuprofen.

Although clinical corroboration is lacking, physicians may have to be prudent in using NSAIDs for patients on low-dose aspirin therapy in whom stable antiplatelet effects are desired. At least, NSAIDs with high sensitivity to COX-2 (diclofenac, etodolac, meloxicam) are preferable when using NSAIDs, given that selective COX-2 inhibitors are not commercially available in Japan. On the other hand, it has been noted that selective COX-2 inhibitors may induce thrombosis by inhibiting prostacyclin production in vascular endothelial cells. In any case, this issue needs to be addressed in a large-scale clinical trial.

4. Aspirin resistance

It has been reported that 10–60% of patients

on aspirin therapy are resistant to aspirin, and such patients are at risk of developing cardiovascular events.[7] Although there may be a number of reasons for this, one that has attracted recent attention is that of increased expression of COX-2, which is hardly present in platelets under normal circumstances. It is speculated that COX-2 shows resistance to aspirin in low-dose aspirin therapy because COX-2 has very low sensitivity to aspirin. In addition, COX genes have more than 100 one-base substitutions, and it is suggested that some of them are associated with structural changes for which aspirin cannot be sufficiently effective. Differences between individuals present an important issue in clinical pharmacology.

Clinical Efficacy of Aspirin

1. Antiplatelet therapy and the aspirin dilemma

A number of clinical trials have been carried out to examine the efficacy of antiplatelet therapy with aspirin or other antiplatelet drugs in the prevention of recurrence and treatment of ischemic vascular injury. Data from the high-quality randomized prospective studies among these trials were analyzed comprehensively using meta-analysis, and the results were published in 1994, as the APT data analysis mentioned at the beginning of this paper. The efficacy of antiplatelet drugs, particularly aspirin, was established by this analysis. Accumulation of data from clinical trials continued, and the results of analysis limited to antiplatelet therapy, including data for the 8 years after APT, were published at the beginning of 2002 by the Antithrombotic Trialists' Collaboration as a revised edition of the APT data.[8]

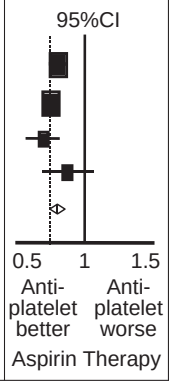
Additional findings on aspirin and other antiplatelet drugs include the following: (1) aspirin significantly prevents cardiovascular events in high-risk patients who have stable angina, intermittent claudication, or atrial fibrillation; (2) prompt use of aspirin in patients with acute myocardial infarction or cerebral infarction is useful, and the preferable acute loading dose is 150–300 mg; and (3) low doses (75–150 mg/day) exert sufficient anti-thrombotic effects and show no marked difference from moderate (160–325 mg/day) or high (500–1,500 mg/day) doses. On the other hand, very low doses of less than 75 mg/day have unstable effects (Table 1).

To overcome the aspirin dilemma, aspirin therapy has been oriented in the direction of lowering doses. However, certain limits to dose reduction have been suggested, and the propriety of low doses of 75–150 mg/day, the current consensus, is considered justified. However, since the efficacy of moderate and high doses, which can cause aspirin dilemma, has been demonstrated, reconsideration of this theory appears necessary.

Table 1 Results of Analysis of the Preventive Effect of Cerebral Vascular Accident in Relation to Aspirin Dose in ATT (Adapted from a figure in reference 8.)

The table shows the results of meta-analysis of controlled studies comparing the incidence rates of cerebral vascular accident for aspirin therapy and placebo control groups of high-risk patients (present or previous arterial thrombosis, stable angina, transient cerebral ischemia, atrial fibrillation). Aspirin at low doses of 75–150 mg showed an adequate preventive effect. Higher doses were also expected to be effective. In contrast, very low doses of less than 75 mg, used in consideration of aspirin dilemma, failed to produce a stable effect. However, the number of very-low-dose cases was too small to deny aspirin dilemma.

Dose (mg/day)	No. of trials with data	Incidence of vascular events (%) ASA	Control	Relative risk	% Odds reduction (SE)
500～1,500	34	14.5	17.2		19 (3)
160～325	19	11.5	14.8		26 (3)
75～150	12	10.9	15.2		32 (6)
＜75	3	17.3	19.4		13 (8)
Any aspirin	65*	12.9	16.0		23 (2)



*Some trials contributed to more than one comparison.

2. Anti-tumor therapy

Based on the fact that the activity of prostaglandin E_2 is increased in colorectal cancer tissues, an inhibitory effect of NSAIDs on the proliferation of colorectal cancer has been suggested. Indeed, epidemiologic data that the incidence of colorectal cancer was lower in aspirin users than in the general population were reported by several researchers.[9] Among these data, the Melbourne Colorectal Cancer Study in 1988 revealed that the incidence of colorectal cancer was 40–50% lower in regular aspirin users than in controls. In addition, a large-scale study performed in 1991 covering 600,000 people showed that the rates of colorectal cancer were 40% and 52% lower in men and women, respectively, who took 16 doses of aspirin per month than in controls.

It became apparent that COX-2 expression is increased in patients with colorectal cancer or familial polyposis. The ability to prevent proliferation and cause regression of colorectal cancer/familial polyposis was also found in other NSAIDs, in addition to aspirin, and it has been considered that such effects are at least partly attributable to COX-2 inhibition by these drugs. In fact, several randomized studies in patients with familial polyposis, who are at high risk of developing colorectal cancer, led to accreditation by the World Health Organization (WHO) of the colorectal cancer-inhibiting agents sulindac, an NSAID with high selective COX-2 inhibitory activity, and selecoxib, a selective COX-2 inhibitor.

In contrast, in the well-known Physicians' Health Study, in which the frequencies of cardiovascular events in male physicians who took aspirin (325 mg every other day) or a placebo for 5 years were followed for 12 years, sub-analysis showed no difference in the incidence of colorectal cancer between the two groups. Currently, a number of clinical trials examining the inhibitory effect of aspirin at a daily dose of 80–600 mg on the development and progression of colorectal cancer in patients with familial polyposis, a high-risk group, are underway, in addition to studies of the efficacy of other NSAIDs. It is expected that the efficacy of aspirin will be better defined within a few years.[9]

In addition, the epidemiologic finding that Alzheimer's disease is less frequent in rheumatic patients who are on prolonged aspirin therapy suggests the diverse potential of the clinical efficacy of aspirin. This may be related to the observed increase of COX-2 expression in microglia cells in the areas surrounding lesions.[10]

Conclusion

Because of its antiplatelet activity for the prevention and treatment of thrombosis, aspirin is one of the most commonly used drugs in the world. However, it has been reported that only one-fourth of all patients with coronary artery disease amenable to aspirin therapy currently use it. If the administration of aspirin to suitable patients is increasingly promoted as recognition by general clinicians is enhanced, aspirin will undoubtedly become the most frequently used drug in the world. No other drug is so inexpensive and has such abundant scientific evidence of its clinical efficacy. However, new questions are arising as the understanding of aspirin deepens, and the potential of its diverse efficacy is staggering. Aspirin, therefore, is not only a well-established therapeutic agent but also an exciting new drug.

REFERENCES

1) Antiplatelet Trialists' Collaboration: Collaborative overview of randomised trials of antiplatelet therapy-I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; 308: 81–106.
2) Schafer, A.I.: Effects of nonsteroidal antiinflammatory therapy on platelets. *Am J Med* 1999; 106: 25S–36S.
3) FitzGerald, G.A. and Patrono, C.: The coxibs, selective inhibitors of cyclooxygenase-2. *N*

Engl J Med 2001; 345: 433–442.
4) Benedek, I.H., Joshi, A.S., Pieniaszek, H.J. *et al.*: Variability in the pharmacokinetics and pharmacodynamics of low dose aspirin in healthy male volunteers. *J Clin Pharmacol* 1995; 35: 1181–1186.
5) Marra, D.E. and Liao, J.K.: Salicylates and vascular smooth muscle cell proliferation: molecular mechanisms for cell cycle arrest. *Trends Cardiovasc Med* 2001; 11: 339–344.
6) Catella-Lawson, F., Reilly, M.P., Kapoor, S.C. *et al.*: Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001; 345: 1809–1817.
7) McKee, S.A., Sane, D.C. and Deliargyris, E.N.: Aspirin resistance in cardiovascular disease: a review of prevalence, mechanisms, and clinical significance. *Thromb Haemost* 2002; 88: 711–715.
8) Antithrombotic Trialists' Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324: 71–86.
9) Thun, M.J., Henley, S.J. and Patrono, C.: Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst* 2002; 94: 252–266.
10) Zandi, P.P., Anthony, J.C., Hayden, K.M. *et al.*: Reduced incidence of AD with NSAID but not H2 receptor antagonists: the Cache County Study. *Neurology* 2002; 59: 880–886.

Vascular Depression

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Abstract: In recent years, a close correlation between cerebrovascular disease and depression in the elderly has become apparent, leading some researchers to advocate for a new entity called "vascular depression (VDep)". Interest in this type of depression has been increasing in Japan. Alexopoulos *et al.* have asserted from the clinical point of view that depression in elderly individuals who have vascular risk factors alone should also be included in the category of VDep. This issue, however, remains controversial. In terms of the mechanisms of onset, one hypothesis based on research into post-stroke depression attributes late-life depression to local lesions, such as left frontal lobe lesions, while the threshold hypothesis explains the onset of depression in patients with silent cerebral infarction in terms of the accumulation of cerebrovascular lesions. However, considering the differences in mechanisms of onset, it would appear desirable to distinguish these two conditions from each other through studies of their pathology. The main treatment is antidepressant therapy, particularly with selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) whose safety and usefulness have been reported. Meanwhile, the prevention and treatment of vascular disease are critical. Also important in this aging society is an understanding of the pathological features and treatment of VDep from the aspect of comprehensive medicine.

Key words: Vascular depression; Post-stroke depression; Late-life depression; Antidepressant therapy

Introduction

Although depression can occur at any age, it is generally considered that the number of elderly individuals with depression will increase sharply as society continues to age. Depression in the elderly is thought to occur through a combination of socio-psychological, organic, and functional factors. In the arena of organic factors, morphological imaging studies that

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Table 1 Diagnostic Criteria for Vascular Depression Proposed by Steffens and Krishnan (1998)

Specify vascular subtype (can be applied to the current or most recent major depressive episode in major depressive disorder or bipolar disorder) if **A** and either **Bl** or **B2** or **B3**:
A. Major depression occurring in the context of clinical and/or neuroimaging evidence of cerebrovascular disease or neuropsychological impairment.
Bl. Clinical manifestations may include history of stroke or transient ischemic attacks, or focal neurologic signs or symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait disturbance, weakness of an extremity).
B2. Neuroimaging findings may include white or gray matter hyperintensities (Fazekas *et al.* 1988 criteria >2; or lesion >5 mm in diameter and irregular in shape), confluent white matter lesions, or cortical or subcortical infarcts.
B3. Cognitive impairment manifested by disturbance of executive function (e.g., planning, organizing, sequencing, abstracting), memory, or speed of processing of information.
The diagnosis is supported by the following features:
1) Depression onset after 50 years of age or change in the course of depression after the onset of vascular disease in patients with onset before 50 years of age. 2) Marked loss of interest or pleasure. 3) Psychomotor retardation. 4) Lack of family history of mood disorders. 5) Marked disability in instrumental or self-maintenance activities of daily living.
(From Steffens, D.C. and Krishnan, K.R.: *Biol Psychiatry* 1998; 43: 705–712)

employ MRI or other imaging techniques led in 1997 to the proposed concept of vascular depression, to describe depression related to cerebrovascular disease. This paper introduces the concept of vascular depression and outlines its treatment.

Concept of Vascular Depression

It has long been indicated that organic factors play a greater role in depression in the elderly. In the 1980s, advances in diagnostic imaging techniques, particularly magnetic resonance imaging (MRI), enabled detailed examination of such involvement, and Krishnan *et al.*[1] reported in 1988 that deep white matter lesions, detected as areas of hyperintensity in MRI studies, were more common in elderly patients with depression than in unaffected elderly individuals. Similar corroborating evidence was obtained by others in the field. In Japan, Fujikawa *et al.*[2] reported a high frequency of silent cerebral infarction in patients with presenile or senile major depression. In 1997, through discussion based on these findings, Krishnan and Alexopoulos proposed that such depression associated with organic cerebrovascular factors be designated "vascular depression," in accord with the concept of vascular dementia prescribed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), published by the American Psychiatric Association.[3]

Krishnan *et al.*[3] reported depression accompanied with cerebrovascular lesions as determined by MRI and not accompanied with neurological signs to be MRI-defined vascular depression. They demonstrated that older age, late age at onset (60 years or older), nonpsychotic subtype, absence of family history of mental disorders, loss of pleasure, and functional disability occurred more often in patients with this type of depression.

Alexopoulos *et al.*[4] investigated patients with depression who were 60 years old or older at onset and who had a history or clinical findings of hypertension or transient cerebral ischemic attack, as a group of elderly patients

with clinically defined vascular depression. These patients were characterized by cognitive dysfunction, disability, retardation, lack of insight and less agitation and limited depressive ideation. Based on these findings, Alexopoulos *et al.* concluded that vascular depression could be identified through clinical features. From these clinical studies, they considered vascular depression to be a broad category of depression related to vascular lesions, and put forth the concept of vascular depression,[5] including depression accompanied with vascular risk factors alone, without evidence on MRI in addition to depression occurring after evident stroke, i.e., post-stroke depression (PSD), and MRI-defined vascular depression as reported by Krishnan *et al.*

However, it has been pointed out that the diagnostic criteria of Alexopoulos *et al.* are not specific to vascular depression, providing no distinction from conventional depression in the elderly. In this connection, Krishnan *et al.* have insisted on the use of diagnostic criteria that place importance on MRI findings. This has resulted in two definitions of vascular depression being employed, namely, that proposed by Alexopoulos *et al.* and that given by Krishnan *et al.* Since controversy exists among researchers as to which definition to use, the concept of vascular depression has yet to be firmly established. This paper presents the diagnostic criteria commonly used in Japan, i.e., those proposed by Steffens and Krishnan,[6] which stress the findings obtained from diagnostic imaging.

In spite of the above-mentioned discrepancy between the definitions of vascular depression proposed by Alexopoulos *et al.* and Krishnan *et al.*, both include PSD in the category of cerebrovascular disease-related depression. However, PSD should be understood from the viewpoint of depression resulting from vascular lesions in specific brain areas and from the aspect of psychological response to physical disorders derived from stroke; this is still a controversial issue in PSD.

On the other hand, the concept of MRI-defined vascular depression was developed from research on depression in elderly individuals with no clinically distinct cerebrovascular disease, and thus it involves no psychological factors such as response to physical disorders in PSD. Therefore, MRI-defined vascular depression may involve different mechanisms of onset from those operating in PSD, and it seems problematic to discuss these types of depression collectively under the single category of vascular depression.

The two conditions should be distinguished from each other through studies of their pathology. It also seems desirable to investigate MRI-defined vascular depression and PSD separately, to avoid confusion in diagnosis.

Pathological Features of PSD

Depression that occurred in the wake of cerebrovascular disease was regarded as PSD in Europe and North America in the latter half of the 1970s, and data from empirical research have continued to accumulate since then. Although survey methods have varied, the average incidences of PSD as determined by DSM criteria in inpatients in the acute stage of stroke are reported to be as follows: major depression, 22%; minor depression (mild depression), 17%.[7] Since about 40% of patients with stroke become depressive, correct recognition and treatment of the condition are extremely important.

Robinson and his colleagues, who are leaders in PSD research, reported in 1981 that depression was more frequent in patients whose lesions were in the left hemisphere, particularly in the left frontal region, than in those whose lesions were in other regions, and that the closer to the frontal pole the forefront of the lesion, the severer the depression.[7] Many reports have corroborated the left frontal lesion hypothesis, but some have indicated a higher incidence of depression in patients with lesions in the right hemisphere or have found

no difference in the incidence of depression, regardless of whether the lesion is located in the right or left hemisphere. Thus, no consensus currently exists among researchers.

To clarify this discrepancy, Robinson's group recently carried out a long-term follow-up study that extended to two years after stroke and focused on the time of observation, i.e., the length of time after stroke, among different studies. According to their report, depression in the acute post-stroke stage was associated with left frontal lesions. In a short-term follow-up of 3–6 months post-stroke, depression was associated with closeness of the lesion to the frontal pole both in patients with right and left hemisphere lesions. A long-term follow-up of 1–2 years post-stroke showed that depression was associated with the size of the lesion and closeness to the occipital pole in patients with right hemisphere lesions.[7] In addition, biological factors were more prominent in the acute stage, whereas socio-psychological factors became involved in the onset of depression in the chronic stage, indicating more complicated determinants of the onset of PSD over the course of time. They reported that the discrepancies among previous reports could be explained by differences in the time after stroke that examinations were conducted in the studies. However, their findings have been challenged, necessitating further investigation.

Mechanisms of Occurrence of Vascular Depression

As mentioned previously, vascular depression is considered to be a heterogeneous entity, including PSD and MRI-defined vascular depression and, according to the diagnostic criteria of Alexopoulos *et al.*, cases that show vascular risk factors. The mechanisms of occurrence of vascular depression are complicated: currently available hypotheses are the local lesion hypothesis attributing onset to left frontal lesions on the basis of PSD studies and the threshold hypothesis obtained from studies of MRI-defined vascular depression. The latter assumes that accumulation of cerebrovascular lesions, rather than the location of cerebral lesions, causes depression by lowering the threshold of disease onset. It is also speculated from previous data that impairment of cortico-striato-pallido-thalamo-cortical circuits, a neuronal network that controls affect, plays an important role in the development of vascular depression.[5]

Treatment of Vascular Depression

As mentioned above, objection has been voiced to the definition of vascular depression proposed by Alexopoulos *et al.*, which includes cases that have vascular risk factors alone. However, their definition may have great value in that it has drawn attention to the importance of prevention and treatment of vascular disease in elderly patients with depression and has contributed to the prevention or improved prognosis of depression in the elderly. The treatment of vascular disease and use of antidepressants or other psychotropic drugs are indispensable for the treatment of vascular depression.

1. Treatment of vascular disease

Although the details are best left to monographs, the control and treatment of hypertension, hyperlipidemia, and diabetes mellitus, all of which are risk factors for cerebrovascular disease, are extremely important. Antiplatelet therapy and anticoagulant therapy are useful for the prevention of recurrent stroke and are therefore necessary for patients with PSD. Their usefulness for the treatment of patients with MRI-defined vascular depression remains to be clarified in future studies. It is of interest that a calcium-channel blocker, nimodipine, has recently been shown to increase the rate of remission and decrease the rate of recurrence of depression when combined with standard antidepressant therapy in patients with vascular depression.[8]

Table 2 Major Reports of Antidepressant Therapy for PSD

Author	N	Rating scale	Design	Medication	Duration	Results
Lipsy *et al.* (1984)	34	HAM-D Zung's SDS	DB/PC	NOR (20–100 mg) PL	4–6 w	NOR>PL
Reding *et al.* (1986)	27	Zung's SDS Barthel ADL	DB/PC	TRZ (50–200 mg) PL	32±6d (TRZ) 25±4d (PL)	TRZ>PL
Lauritzen *et al.* (1994)	20	HAM-D MES	DB	IMP+MIA (mean 75+25 mg) DMI+MIA (mean 66+27 mg)	6 w	IMP>DMI
Andersen *et al.* (1994)	66	HAM-D MES	DB/PC	CPM (10–40 mg) PL	6 w	CPM>PL
Gonzalez-Torrecillas *et al.* (1995)	48	HAM-D Barthel ADL	Open	FLX (20 mg), NOR (25–75 mg) Untreated	6 w	FLX, NOR>untreated
Dam *et al.* (1996)	52	HAM-D Barthel ADL	DB/PC	MAP (150 mg), FLX (20 mg) PL	3 m	FLX>MAP>PL
Wiart *et al.* (2000)	31	MADRS	DB/PC	FLX (20 mg) PL	45 d	FLX>PL
Robinson *et al.* (2000)	104*	HAM-D	DB/PC	FLX (10–40 mg), NOR (25–100 mg), PL	12 w	NOR>PL≈FLX
Kimura *et al.* (2002)	12	HAM-D	Open	MIL (30–75 mg)	6 w	Remission rates 70% (continuing cases) 58% (all cases)

HAM-D: Hamilton Depression Rating Scale, Zung's SDS: Zung's Self-Rating Depression Scale, Barthel ADL: Barthel Activities of Daily Living Index, MES: Melancholia Scale, MADRS: Montgomery-Asberg Depression Rating Scale, DB: double-blind, PC: placebo control, PL: placebo, NOR: nortriptyline, TRZ: trazodone, IMP: imipramine, DMI: desipramine, CPM: citalopram, FLX: fluoxetine, MAP: maprotiline, MIA: mianserin, MIL: milnacipran, *Includes 48 non-depressive patients.
(From Kimura, M.: *Rinsho Seishin Yakuri* 2002; 5(11): 1549–1556.)

2. Treatment with psychotropic drugs

Reports on psychotropic drug therapy for vascular depression focus mainly on patients with PSD. Drugs effective for PSD, in which cerebral organic involvement is prominent, are generally considered to be effective for vascular depression as a whole. Table 2 shows major overseas studies on the psychotropic drug therapy reported to date.[9] The usefulness of the secondary amine nortriptyline, a tricyclic antidepressant, has often been reported. The efficacy of trazodone, which is associated with fewer anticholinergic side effects, has also been reported. However, it has been pointed out that delirium and over-sedation are not unusual as adverse reactions to these drugs.

Selective serotonin reuptake inhibitors (SSRIs) are reported to be associated with fewer adverse reactions of this kind than conventional antidepressant drugs, and the usefulness of citalopram and fluoxetine (both unavailable in Japan), two drugs of this class, has been documented through several studies. The usefulness of sertraline, another SSRI, in the treatment of vascular depression has also been reported, suggesting that SSRIs are promising therapeutic options. However, it has been noted that SSRIs may cause gastrointestinal symptoms such as nausea and diarrhea in the early phase of therapy. Since adverse reactions are more likely to be induced in patients with vascular depression who have vulnerability in the brain, it is important that medication with any antidepressant drug be initiated at a low

dose and increased gradually, while exercising caution as to possible adverse reactions.

Methylphenidate, a psycho-stimulant, is also reported to be effective and fast acting, but careful examination is required in regard to its efficacy and safety, including the issue of dependence.

We recently carried out a study to investigate the therapeutic effects of milnacipran, a serotonin and noradrenaline reuptake inhibitor (SNRI), on post-stroke depression, and observed high therapeutic efficacy at doses as low as 30–75 mg/day. Concomitant use of antihypertensive drugs or other cardiovascular drugs is particularly common in patients with vascular depression. In this regard, milnacipran, which is known to have fewer interactions with other drugs, is advantageous for this condition.[10)]

Therefore, physicians treating vascular depression should first use the SNRI milnacipran or an SSRI, and consider the use of nortriptyline if the response to these therapies is inadequate.

Conclusion

Depression in which cerebrovascular disease is involved as a factor is known as vascular depression. However, the diagnostic criteria for this entity remain controversial. The concept of vascular depression includes PSD involving clinically evident cerebrovascular disease and depression involving silent cerebral infarction. These two conditions, however, may differ in pathological features, including mechanisms of onset, and thus need to be dealt with separately. From the therapeutic aspect, this concept is of value in that it has drawn attention to the prevention and treatment of vascular disease in elderly patients with depression. SNRIs and SSRIs are thought to be promising therapeutic options in antidepressant therapy.

REFERENCES

1) Krishnan, K.R., Goli, V., Ellinwood, E.H. *et al.*: Leukoencephalopathy in patients diagnosed as major depressive. *Biol Psychiatry* 1988; 23: 519–522.
2) Fujikawa, T., Yamawaki, S. and Touhouda, Y.: Incidence of silent cerebral infarction in patients with major depression. *Stroke* 1993; 24: 1631–1634.
3) Krishnan, K.R., Hays, J.C. and Blazer, D.G.: MRI-defined vascular depression. *Am J Psychiatry* 1997; 184: 497–501.
4) Alexopoulos, G.S., Meyers, B.S., Young, R.C. *et al.*: Clinically defined vascular depression. *Am J Psychiatry* 1997; 154: 562–565.
5) Alexopoulos, G.S., Meyers, B.S., Young, R.C. *et al.*: 'Vascular depression' hypothesis. *Arch Gen Psychiatry* 1997; 54: 915–922.
6) Steffens, D.C. and Krishnan, K.R.: Structural neuroimaging and mood disorders: recent findings, implications for classification, and future directions. *Biol Psychiatry* 1998; 43: 705–712.
7) Robinson, R.G.: *The Clinical Neuropsychiatry of Stroke*. Cambridge University Press, Cambridge, 1998 (Translation in Japanese supervised by Endo, S. and Kimura, M.: Nosotchu ni okeru rinsho shinkei igaku. Seiwa Shoten, Tokyo, 2002). (in Japanese)
8) Taragano, F.E., Allegri, R., Vicario, A. *et al.*: A double blind, randomized clinical trial assessing the efficacy and safety of augmenting standard antidepressant therapy with nimodipine in the treatment of 'vascular depression'. *Int J Geriatr Psychiatry* 2001; 16: 254–260.
9) Kimura, M.: Concept of vascular depression and its drug therapy. *Rinsho Seishin Yakuri* 2002; 5(11): 1549–1556. (in Japanese)
10) Kimura, M., Kanetani, K., Imai, R. *et al.*: Therapeutic effects of milnacipran, a serotonin and noradrenaline reuptake inhibitor, on post-stroke depression. *Int Clin Psychopharmacol* 2002; 17: 121–125.

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