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Review

Pathophysiology of clinical benign prostatic hyperplasia

Keong Tatt Foo

Department of Urology, Singapore General Hospital, Singapore

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Abstract A disease can be defined as an abnormal anatomy (pathology) and/or function (physiology) that may cause harm to the body. In clinical benign prostatic hyperplasis (BPH), the abnormal anatomy is prostate adenoma/adenomata, resulting in a varying degree of benign prostatic obstruction (BPO) that may cause harm to the bladder or kidneys. Thus clinical BPH can be defined as such and be differentiated from other less common causes of male lower urinary tract symptoms. Diagnosis of the prostate adenoma/adenomata (PA) can be made by measuring the intravesical prostatic protrusion (IPP) and prostate volume (PV) with non-invasive transabdominal ultrasound (TAUS) in the clinic. The PA can then be graded (phenotyped) according to IPP and PV. Multiple studies have shown a good correlation between IPP/PV and BPO, and therefore progression of the disease. The severity of the disease clinical BPH can be classified into stages from stage I to IV for further management. The classification is based on the effect of BPO on bladder functions, namely that of emptying, normal if post-void residual urine (PVRU) $<$ 100 mL; and bladder storage, normal if maximum voided volume (MVV) $>$ 100 mL. The effect of BPO on quality of life (QoL) can be assessed by the QoL index, with a score $\geq$3 considered bothersome. Patients with no significant obstruction and no bothersome symptoms would be stage I; those with no significant obstruction but has bothersome symptoms (QoL $\geq$ 3) would be stage II; those with significant obstruction (PVRU $>$ 100 mL; or MVV $<$ 100 mL), irrespective of symptoms would be stage III; those with complications of the disease clinical BPH such as retention of urine, bladder stones, recurrent bleeding or infections would be stage IV. After assessment, further management can then be individualised. A low grade and stage disease can generally be watched (active surveillance) while a high grade and stage disease would need more invasive management with an option for surgery. The final decision making would take into account the patient's age, co-morbidity, social economic

E-mail address: foo.keong.tatt@singhealth.com.sg.
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background and his preferences/values. Proper understanding of pathophysiology of clinical BPH would lead to better selection of patients for individualised and personalised care and more cost effective management.

1. Introduction

A disease is an abnormal pathophysiological state or condition that may cause harm to the organism. It is important to distinguish between the cause and consequence of a disease. For example, diabetes mellitus is caused by an abnormal insulin metabolism which results in an elevated postprandial sugar level. High blood sugar level by itself is not diabetes mellitus. Similarly in clinical benign prostatic hyperplasia (BPH), benign prostatic obstruction (BPO) [1] is the consequence rather than cause of the disease. What then is the abnormal anatomy (pathology) that causes abnormal functions (physiology) in clinical BPH and may eventually harm the patient? Our study showed that prostate adenoma/adenomata (PA) is the cause of clinical BPH, resulting in a varying degree of obstruction with or without symptoms [2]. If the obstruction is severe, it may eventually harm the bladder and the kidneys. Intervention would therefore be needed to prevent this.

In clinical practice, the need for intervention depends on whether the disease is: first, life threatening; second, affecting the functions of organs; and last, affecting the patient's quality of life (QoL), in order of priority. Though clinical BPH is seldom life threatening, severe obstruction leading to hydronephrosis, and infection in an immunocompromised patient may cause death. More commonly, bladder functions may be affected leading to poor voiding and back pressure changes in the kidneys, compromising their functions. When making the final decision on treatment modality (watchful waiting, medical or surgical intervention) for a particular patient, age, co-morbidity, social economic background, and patient preferences or values should also be considered. Thus experience and an understanding of the pathophysiology of the disease are important in reaching a final balanced clinical decision for personalised care of the individual patient [3].

2. Definition of clinical BPH

On histopathology, BPH is nodular hyperplasia and not diffuse hyperplasia, affecting the transitional and periurethral zones of the prostate [4]. Often the hyperplasia is multinodular, coalescing to form adenomata. Adenomata from the transitional zone form the lateral lobes while adenomata from the periurethral zone form the middle lobe in clinical disease [5]. BPH gives rise to obstruction by compression as well as by distortion of the bladder outlet. In flow dynamics, distortion causes more obstruction than compression. Using the analogy of a garden hose, it is easier to stop the water flow by distorting (bending) rather than compressing the hose. At the prostate, the lateral lobes tend to compress the bladder outlet while the middle lobe tends to distort it.

A third factor which may play a part in bladder outlet obstruction (BOO) is the decrease in elastic system fibers and collagen in the prostatic urethra [6]. There may also be an increase in chondroitin sulphate proteoglycans in BPH [7]. These may affect the plasticity of the prostatic urethra, influencing the distortion and compression by the PA. This may explain why in some older patients, the prostate can grow to a large size with minimal obstruction, possibly because the prostatic urethra becomes more rigid or less elastic and therefore more difficult to bend or compress.

The degree of BOO depends more on where the PA is sited than its size. Adenoma sited at the bladder neck in the periurethral zone forming the middle lobe would distort the bladder outlet and cause severe obstruction even if small, while adenoma sited deep in the transitional zone forming the lateral lobes would need to grow to a much bigger size before causing compression of the prostatic urethra and obstruction (Figs. 1 and 2).

BPH progresses slowly and patients may accommodate to it, not having symptoms even though they may have severe obstruction. Thus clinical BPH can be defined as PA irrespective of size, causing a varying degree of obstruction, with or without symptoms [2].

3. Diagnosing clinical BPH

In a normal male, the bladder neck is inverted with the prostate less than 20 g and peak flow rate above 20 mL/s [2]; but in a patient with clinical BPH, the bladder neck is distorted by the PA, and where the PA is sited gives rise to its shape. This can be detected by measuring the intravesical prostatic protrusion (IPP) on transabdominal ultrasound (TAUS). IPP can be measured from the tip of the protruding prostate to the base of the gland at the circumference of the bladder, seen in the sagittal plane of the TAUS [8,9] (Fig. 3). It can be considered as a simple measure of the prostate shape, and can be graded accordingly: grade 1, $\leq$5 mm; grade 2, $>$5–10 mm; and grade 3, $>$10 mm [9]. IPP has 100% specificity and 100% positive predictive value in the diagnosis of clinical BPH [2]. Thus clinical BPH can be diagnosed with confidence by measuring IPP with TAUS and uroflowmetry [10].

In the family physician clinic, clinical BPH can be suspected on digital rectal examination if the prostate is more than 2 finger breadths and has a smooth firm consistency, and the patient has a poor average flow rate [11].