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PERSPECTIVE

Solving the benign prostatic hyperplasia puzzle



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1. Introduction

Benign prostatic hyperplasia (BPH) is a common urological condition, and yet there are many puzzles waiting to be solved. This perspective is to help explain some of these puzzles, based on our recent publications and previous clinical studies on BPH.

2. Why small prostates obstruct and some big prostates do not obstruct?

Clinical BPH as a disease has been defined as benign prostatic enlargement (BPE) [1,2]; however in clinical practice we still see many patients with no enlargement, with prostate volume less than 20 g still causing symptoms and obstruction [3]. How can this be explained?

To solve the puzzle, we first need to redefine clinical BPH.

We need to go back to the basic fundamental pathology of BPH, which on histology is described as nodular hyperplasia [4], not diffused hyperplasia of the whole gland. The nodular hyperplasia forms nodule (adenoma) or more often multiple nodules or adenomata (PA). The PA affects mainly the transitional zone and the periurethral zone of the prostate. The transitional zone PA gives rise to the lateral lobes while those in the periurethral zone give rise to the middle lobe. As the prostate gland is situated around the bladder neck, the PA would cause a varying degree of obstruction, depending on the site of the PA. The lateral

lobes PA would cause compression of the prostatic urethra while the middle lobe would distort the funneling effect of the normal urethral vesical angle, and cause more severe obstruction. This can be explained by flow dynamics, that distortion causes more severe obstruction than compression. As in the example of using the garden hose, bending the hose (distortion) would stop the flow more effectively than trying to compress it.

The degree of obstruction also depends on whether the PA is situated below the sub mucosal layer, or deeper in the stroma of the prostate. PA in the sub mucosal layer, even when small, would cause obstruction early, while the PA in the stroma would need to grow to a bigger size to cause obstruction. This would explain why PA can cause obstruction even when small, and may not cause obstruction even when big.

3. The subcervical adenoma in patients with a small prostate

This is typically seen in younger patients in the late forties or early fifties with a history of poor flow and other lower urinary tract symptoms (LUTS). The PA elevates the bladder neck high and causes obstruction. This condition is still called a high bladder neck in the literature, but with better understanding of the BPH pathology, it is more often due to the PA sitting below the bladder neck, and is not a primary bladder neck problem [5].

4. Classical median lobe

If the PA arising from the periurethral zone grows into the bladder, this would give rise to the classical median lobe,

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which causes ball valve obstruction. The lateral lobe may be small without PA, or may also have PA, giving rise to trilobular obstruction.

Our recent study confirms that of 73 patients with PA, 39 had lateral lobes obstruction, 12 middle lobes and 22 had trilobular obstruction, and the average flow rate was 16.0 mL/s, 11.9 mL/s and 8.9 mL/s respectively [5].

The above would substantiate our definition of clinical BPH that clinical BPH is an adenoma or adenomata (PA), irrespective of size, and it causes a varying degree of obstruction.

5. What is the relationship between clinical BPH and LUTS?

Can we treat LUTS/BPH by the symptoms score alone as in many clinical guidelines? Why do we need to treat clinical BPH?

Clinical BPH (PA) is a slow progressive disease that causes obstruction and may eventually cause dysfunctions of the bladder and kidneys, therefore the need to treat when the functions of the bladder are threatened. If not, the condition can still be watched.

The other reason for treatment would be to relieve bothersome symptoms. Whether the symptoms bother the patient and whether the patient wants treatment would be his choice. He needs to know the effectiveness of the treatment and its side effects to make an informed decision.

Many studies have shown that there is a poor correlation between the International Prostate Symptoms Score (IPSS) and obstruction by PA. In a study done by Rosier et al. [6], of 717 patients studied, 55 patients had a mild symptoms score of IPSS 0–7, 49% of these patients were not obstructed and 51% were still obstructed.

In our own study on 79 patients with acute retention of urine, 36.5% had only mild symptoms before the acute episode. Of the initial 150 patients, 6.7% had hydro-nephrosis due to chronic retention [7]. In another study by Chia et al. [8] of 200 patients with pressure flow studies (PFS) done, 57% of patients with severe IPSS of 21 or more were obstructed, but 43% of them were not obstructed. Thus patients with PA can have severe obstruction with minimum or no symptoms. While many of those with severe IPSS may not be obstructed.

Therefore, BPH can further be defined as prostate adenoma, causing a varying degree of obstruction, with or without LUTS [5].

BPH should not be treated by the severity of IPSS alone, as that would lead to over treatment and under treatment with regard to obstruction.

6. Classifying severity of BPH (PA)

BPH should be treated by considering both the symptoms and obstruction. Obstruction would be significant if it causes the dysfunctions of the bladder, that of storage and voiding. If the voiding function is affected, there will be persistent post void residue urine, with 100 mL used as a cut-off. If there is a storage problem, the patient will have urinary frequency and low maximum voided volume, less

than 100 mL. The bothersome symptoms index (quality of life, QoL) is more important than the IPSS in symptoms assessment, with a QoL ≥ 3 considered bothersome. Thus the severity of clinical BPH can be classified according to the stage of the disease [9] and this has been shown to be feasible [10].

Stage I: patient with no bothersome symptoms and no significant obstruction;

Stage II: patient with bothersome symptoms but no significant obstruction;

Stage III: patient with significant obstruction with or without bothersome symptoms;

Stage IV: patient with complications of BPH such as retention of urine, persistent macro haematuria, stones and UTI.

Going back to basic good clinical practice, treatment should be decided according to the severity of the disease. Thus stage I patients can be managed conservatively with reassurance, fluid adjustment and exercise. Stage II patients may need medication with alpha blockers, and for those with large prostates more than 30 g, 5 Alpha Reductase Inhibitors (5 ARI's). For stage III patients, surgery would be an option. Treatment with 5 ARI's or in combination with alpha-blockers could be initiated and the patients followed up closely. Stage IV patients would generally require surgery [11].

From our experience with 408 patients assessed with the above, we have shown that staging is useful in managing patients with LUTS and BPH [12].

However, the diagnosis has to be confirmed before treatment, especially surgical intervention.

7. Diagnosis of clinical BPH (PA)

Diagnosis of PA can be done confidently with non-invasive transabdominal ultrasound in the clinic, looking for the intravesical prostatic protrusion (IPP) in the sagittal view. IPP is the distance in mm from the inner most tip of the protrusion to the base of the prostate, at the circumference of the bladder [13].

The IPP is 100% specific and has 100% positive predictive value for diagnosing PA in our study [5]. But its negative predictive value is low at 36%.

The urinary flow rate would help to further differentiate PA from other causes of LUTS. A diagnosis of no PA or normal prostate can be made clinically for patients with no IPP and a good flow rate greater than 20 mL/s [14]. Poor flow in patients with no IPP can be due to PA in the prostatic urethra or detrusor underactivity, and a urodynamics study or flexible cystoscopy would have to be done to determine the cause.

On the other hand, patients with good flow can still have PA. In our recent study of patients with a good flow rate of more than 12.5 mL/s, 65% of patients with grade 3 IPP were still obstructed based on PFS [15].

With the above understanding, male LUTS can be differentiated into those with PA and those without, and they can then be managed separately.

8. PSA does not increase with age

If a patient has no PA, no prostate cancer and no prostatitis, his prostate specific antigen (PSA) should be less than 1 µg/L, and the value does not increase with age.

A normal prostate PSA is less than 1 µg/L. This is suggested in our study of patients with PA with varying pre-operative PSA. Postoperatively, after the enucleation procedure with total removal of the adenoma, the PSA is generally less than 1 µg/L [16]. Also, we have patients in the clinics with LUTS but no PA as defined, and their PSA does not increase with age on long term follow up, some up to 15–20 years (unpublished data).

Why should PSA increase with age in the normal prostate?

Previous studies suggesting that PSA increased with age is due probably to the original cohort of subjects with no prostate cancer, but many of them would have a varying degree of BPH (PA), thus causing the PSA to be higher than 1 µg/L. As the PA progresses with age, the PSA would appear to increase with age.

For persons with a normal prostate, prostate volume less than 20 g, no IPP and good flow, the PSA remains the same over the years and does not increase with age.

9. Grading of IPP

The IPP can be graded according to the degree of protrusion, with grade 1: ≤5 mm; grade 2: 6–10 mm and grade 3: >10 mm.

The grade of IPP is strongly correlated to the urodynamic evidence of obstruction. For patients with grade 1 IPP, 21% are obstructed, whereas for patients with grade 3 IPP, 96% are obstructed [8].

This would explain why IPP can predict the failure rate of trial off catheter in patients with acute retention of urine, with 36% failure rate for grade 1 and 67% failure rate for grade 3 IPP [13]. IPP can also be used to predict the progression of clinical BPH. In our study of patients with a mean follow-up of 32 months, 6% of patients with grade 1 IPP and 44% of grade 3 IPP would deteriorate in terms of worsening symptoms, developing PVR and requiring surgery [17]. Our study also showed that IPP is a better predictor of obstruction (on PFS), than PSA and prostate volume, with area under the curve (AUC) of 0.77 vs. 0.70 vs. 0.63, respectively [18].

In our study of 408 patients, 31% of patients had grade 3 IPP and the majority 69% had grade 1 and 2 IPP. This would explain why the majority of patients with LUTS/BPH do not deteriorate [12]. In one study of 105 patients with prostatism presumably due to BPH, only 16% deteriorated, of which 9% required surgery after 5 years of follow-up. Eighty-four percents remained the same or better [19].

Patients with persistently high residual urine more than 100 mL and high grade prostate would require surgery [11]. Using the staging and grading system for BPH, 9% of patients in that study required transurethral resection of the prostate (TURP), 32% were treated medically and 59% were advised conservative management with fluid adjustment and lifestyle changes [12]. This conformed closely with the

natural history of BPH, suggesting that patients were not over treated or undertreated.

10. Conclusion

With the redefinition of BPH, that it is essentially an adenoma or multiple adenomata, many of the puzzles of BPH can be solved and explained. Why some small prostate obstruct even when small, and big prostates do not obstruct is dependent on the location of the PA. Patients with LUTS can be differentiated by whether they have PA or no PA with non invasive transabdominal ultrasound and uroflowmetry. Cost effective treatment can then be individualized, according to the grade and stage of the disease.

Conflicts of interest

The authors declare no conflict of interest.

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