Benign prostatic hyperplasia- clinical features and diagnosis

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Introduction

Benign Prostatic Hyperplasia (BPH) will develop in around 50% of men over the age of 60 years[1] resulting in a prostate which is measurably larger than normal. In around 25%[2] of men lower urinary tract symptoms (LUTS) will accompany BPH and this figure increases significantly in older men. These symptoms are partially attributable to an enlarged prostate as well as other, co-morbidities such as cardiac disease, renal disease and neuromuscular changes within the bladder.

Function of the prostate

The normal prostate gland is around 4cm in diameter[3] with an average weight of 20g[4], it is located inferior to the urinary bladder. It is a "doughnut" shaped organ which encircles the prostatic urethra. The location and orientation of the prostate is directly related to the development of LUTS with enlargement contributing to alteration in urinary flow rates and ultimately, in some patients, leading to acute urinary retention.

The prostate contributes mildly acidic secretions which make up around 25% of the seminal volume. These secretions ultimately improve the chances of sperm reaching and fertilising an egg by providing the following:

- Citric acid and fructose used in oxidative metabolism, which provides sperm with energy;
- Proteolytic enzymes such as prostate specific antigen, pepsinogen and hyaluronidase which help facilitate sperm motility via liquefaction of seminal fluid;
- Seminalplasmin which contributes to sperm motility and also has potent antimicrobial activity, and thus reduces the number of naturally occurring bacteria in the ejaculate itself and the lower section of the female reproductive tract.

An important component of prostatic secretions is prostate specific antigen (PSA), a protease enzyme involved in promoting motility of sperm. PSA is a measurable marker within the serum and is associated with both benign and malignant prostatic hyperplasia. It is used in the diagnosis and monitoring of prostate cancer but is insufficiently reliable as a marker to allow for widespread screening. Some men with BPH may have a high PSA; others with early malignant disease may have a low PSA, thus a low PSA does not rule out malignant disease. Due to this lack of specificity it is difficult for practitioners and men to make informed decisions based upon a PSA result alone. In addition, the investigations which are undertaken subsequent to the identification of a potentially abnormal PSA are not without complications. What we do know is that PSA rises with age and in line with glands that are increasing in size.

Pathophysiology

The aetiology and pathophysiology of BPH are still largely unclear. Whilst there is no doubt that ageing has a significant role there are also a number of other factors which appear to be associated with the development of BPH. The development of BPH should be considered to be the result of the conflation of the concepts discussed below with each one, possibly contributing, to the overall outcome. Clearly identification of these mechanisms is essential in terms of developing interventions which may ultimately reduce the health burden associated with BPH.

Age

There is overwhelming evidence to suggest that as men age there is an increase in the size of the prostate and the incidence of lower urinary tract symptoms.[5] Some studies investigating men without prostate cancer have shown an increase in prostatic volume of 2.5% per year[6]. There is not though, a direct relationship between the size of the prostate and the severity of LUTS[7]. As detailed above BPH is not the only contributory factors to the development of LUTs, rather it is part of a set of issues some of which are age related and ultimately affect the voiding and storage of urine. Urinary flow rates also decline with age with men over the age of 70 years of age showing a more rapid decline[8]. There is also evidence to suggest that age is also associated with the development of BPH and this is irrespective of whether or not men exhibit symptoms; more than 90% of men have histopathological changes consistent with BPH.

Tissue remodelling and age

There is evidence of a tissue-remodelling process behind these age-related changes where basal cells in the prostate become hypertrophic. These changes are observed as a result of alterations in cell-signalling between stromal and epithelial cells with a shift from paracrine control to autocrine control causing the epithelial cells begin to be in control of the production their own growth factors. In addition, the balance of cell proliferation and apoptosis shifts in favour of proliferation. Increased expression of transforming growth factor (TGF)-β1 and Bcl-2 may explain this shift; both are involved in the normal apoptotic control mechanisms within the prostate. Research on BPH tissue has demonstrated that the apoptotic index is higher in normal cells than in BPH cells; the same work also shows an increase in the proliferative index with regard to the BPH tissue[9]. Ultimately, the net effect of this this process is that BPH cells become hypertrophic and survive longer compared to those in a healthy prostate.

Hormonal effects

Men who castrated before puberty or who have a genetic deficiency in 5-α reductase do not develop BPH.[10] Androgens do not directly cause BPH, but contribute to its development as a process. The metabolite of testosterone, dihydrotestosterone (DHT), is generated via the action of 5-α reductase, which is secreted from stromal and basal epithelial cells. Some studies have demonstrated elevated DHT activity in BPH tissue when compared to normal tissue[11] as well as elevated expression of a number of androgen dependant genes. The actual effect of this altered androgen activity is yet to be fully clarified and in some areas of the literature has not been observed when examining fresh BPH tissue.

The effects of oestrogen have also been studied, but to a lesser extent than androgens. As men age their levels of circulating oestrogen remain constant; however, factors such as background of age-related declining levels of testosterone, excessive amounts of body fat can cause elevations in circulating oestrogen due to increased levels of aromatase. Oestrogen stimulation can drive either proliferative effects, mediated at the oestrogen receptor alpha (ER-α) or proliferative regulation and apoptotic effects mediated by the oestrogen receptor beta (ER-β). It has been observed that BPH tissue has a relative up-regulation of the ER-α receptor thus using the altered ratio of androgen to oestrogen seen in the ageing male to stimulate growth[12].

Metabolic effects

There is a link between metabolic syndrome and BPH. Men with elevated blood pressure, insulin, obesity and low levels of high density lipoprotein cholesterol (HDL-C) have been shown to have faster growing BPH[13]. Equally, and within this group, men with BPH and metabolic syndrome demonstrated faster growth rate of the prostate when compared to those who had BPH alone. This study also demonstrated that men with BPH and metabolic syndrome had higher BMI, body weight, serum glucose, triglyceride, PSA and lower HDL-C when compared to those patients who had BPH only[14]. There appears to therefore be a link with metabolic disruption and possibly Type-2 diabetes and the speed of development and severity of symptoms in BPH.

Inflammation

The action of inflammation as a mechanism for growth within the prostate has been investigated by a number of studies[15, 16]. BPH tissue has been identified as having evidence of chronic inflammation and that the tissue with higher levels of inflammation was from larger prostates with higher PSA levels. It is suggested that constant inflammatory activity and subsequent cytokine release leads to cell destruction and the subsequent triggering of a healing response. This healing response is closely related to the hyperproliferative effects seen within enlarged prostate glands. This proliferative environment has also been shown to give rise to hypoxia based upon local demands for oxygen by growing cells. This directly promotes angiogenesis and growth in response to a number of growth factors including vascular endothelial growth factor (VEGF).

It is likely that BPH develops as a consequence of a number of these interplaying factors including ageing, inflammation, hormonal changes and metabolic consequences. What is important is that all of these factors include significant targets for drugs. As work on elucidation of the exact cause of BPH becomes more advanced it is hoped that a treatment will be discovered that targets the underlying pathophysiology behind this condition.

Symptoms

BPH does not always present with symptoms. Indeed, in the current public health context with regard to prostate cancer many men may present to their GP for a prostate examination or have such checks conducted as part of “well-man” type intervention. Equally, for those patients who prefer not to seek medical advice, or who accept symptoms as an unavoidable consequence of the ageing process, the pharmacist can be an invaluable member of the healthcare team in terms of education and initial assessment for patients who may have more complex problems.

Most patients present with LUTS, although there is a lack of convincing evidence to relate prostate size to severity of LUTS. As stated previously, there are other contributing factors to the development of these symptoms. This is notable from the fact women present with LUTS and in both cases there is age-related changes observed in smooth muscle and therefore the subsequent effect that has upon the function of the bladder and associated structures.

The typical presentation of a patient with BPH is detailed below:

- Voiding symptoms:
  - Hesitancy, associated with resistance to flow and possibly weak muscle contractions;
  - Poor urinary flow and associated increase in the time taken to urinate;
  - Incomplete bladder emptying and the need to visit the toilet on multiple occasions because of this feeling.
  - Terminal dribbling:
- Storage symptoms;
  - Urgency, the need to void without the ability to control. May be associated with urge incontinence where urine is involuntary leaked;
  - Polyuria during the day and at night.

These symptoms are associated with both a resistance to flow caused by an enlarged prostate or possibly by weak or overactive detrusor muscle. In relation to voiding symptoms, the majority could be attributed to a weak detrusor and/or the need to overcome resistance to flow. Conversely, storage symptoms are associated with possible over activity of the detrusor muscle or by BPH.

A proportion of men will develop urinary retention associated with BPH. This can be acute and is usually very painful; it is resolved, in the short-term, with the introduction of a urinary catheter. Patients may also present with chronic retention where a painless but palpable bladder can develop over an extended period of time giving rise to the potential for renal failure, hypertension and chronic infection. Once catheterised, these patients may then suffer a significant loss of urine which could lead to electrolyte imbalance. In both acute and chronic retention, patients are often referred for prostatectomy, which associated with surgical risks and complications of urinary incontinence and sexual dysfunction. In the case of acute retention, emergency surgery may be required, which has significantly higher risks of surgical complications than elective surgery for chronic retention.[1]

Diagnosis

The severity of LUTS on presentation is quantified using the International Prostate Symptom Score. This is an eight question tool originally created in 1992 by the American Urological Association. It asks patients to rate their urinary symptoms on a 1-5 scale and also to rate the effect of the symptoms on their quality of life using a 1-6 scale. The scores are then quantified as follows:

- 0-7- mild LUTS
- 8-19 moderate LUTS
- 20-35 severe LUTS

The NICE guidance, published in May 2010 makes specific recommendations as to how patients should be managed on initial presentation[17]. This includes:

- Assessment of general medical history to identify causes which includes identifying other co-morbidities and determining the what medication the patient takes;
- Physical examination, including assessment of the bladder and a digital rectal examination (DRE);
- Urine dipstick test to detect blood, glucose, protein, leucocyctes and nitrites - all of which are focussed on identifying infection or haematuria;
- Completion of a urine frequency chart;
- Assessment of serum creatinine if renal impairment is suspected. This is typically patients with a palpable bladder or who have had recurrent urinary tract infections which is indicative of chronic urinary retention.

Following initial assessment, patients can be offered lifestyle advice should their LUTS not be particularly troublesome. In many cases, assessment of fluid input/output may help to identify changes in lifestyle which may subsequently improve symptoms. Simple observations of how fluid intake affects symptoms may be particularly useful, this could relate to both timing and volume of intake. Equally, identification of medication which could exacerbate the condition, including any OTC or herbal medication may help symptoms, particularly in the case of sympathomimetic drugs which may worsen urinary retention.

Patients who have a positive digital rectal examination (DRE) may wish to have their PSA tested in order to rule out the potential of prostate cancer. In such cases, patients should be counselled with regard to the specificity of PSA testing. Other features such as feel of the prostate on DRE may help guide a decision with regard to PSA testing; a smooth, evenly enlarged prostate is less likely to be cancerous compared to one which is irregular and has hard nodules. Patients with an abnormal DRE and/or an elevated PSA may be referred for specialist assessment which may include a transrectal ultrasound. This is also used if biopsy of the prostate is necessary in terms of guiding sample collection.

Patients with LUTS necessitating specialist referral are recommended to undergo flow studies and urodynamics. Primarily this is to help identify which patients will respond best to surgical intervention. Patients, who have outflow obstruction and low flow rates predominantly voiding symptoms, respond well to surgical intervention, while those who demonstrate a pattern of storage symptoms where there is a higher flow rate do not.[18, 19] The identification of a low flow rate is important in terms of diagnosing a bladder outflow obstruction. Patients with low flow rates of <10 mL/s can be reliably diagnosed as having an obstruction to bladder outflow whereas those with flow rates>15 mL/s are more likely to be demonstrating storage symptoms associated with an overactive detrusor muscle.

Some patients who exhibit haematuria and symptoms of chronic infection of the upper urinary tract including significant pain may be referred for cystoscopy to rule out any other abnormality beyond BPH.

Conclusion

BPH is a contributory factor to the development of LUTS, which can significantly affect the quality of life for many men. The exact cause of the disease is unknown but there is a body of research that is gradually elucidating the pathological mechanisms at work. Pharmacists can have a significant role in

identifying and supporting those people who may need simple advice and support and those who should be referred for intervention. There is evidence that patients are willing to tolerate significant LUTS because of a lack of desire to contact medical help, clearly pharmacists are an accessible and alternative source of help for such patients.

References

1. Thorpe A, Neal D. Benign prostatic hyperplasia. Lancet. 2003; **361**(9366): 1359-67.
2. McNicholas T, Kirby R. Benign prostatic hyperplasia and male lower urinary tract symptoms (LUTS). Clin Evid (Online). 2011; **2011**.
3. Jenkins GW, Kemnitz CP, Tortora GJ, Tortora GJCc. Anatomy and physiology : from science to life. 2nd ed., International student ed. Hoboken, N.J.: Wiley. 2010.
4. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol. 1984; **132**(3): 474-9.
5. McNicholas T. Benign Prostatic Hyperplasia. Surgery. 2011; **29**(6): 282-6.
6. Loeb S, Kettermann A, Carter HB, Ferrucci L, Metter EJ, Walsh PC. Prostate volume changes over time: results from the Baltimore Longitudinal Study of Aging. J Urol. 2009; **182**(4): 1458-62.
7. Fitzpatrick JM, Krane RJ. The Prostate: Churchill Livingstone; 1989.
8. Jacobsen SJ, Jacobson DJ, Girman CJ, Roberts RO, Rhodes T, Guess HA, et al. Treatment for benign prostatic hyperplasia among community dwelling men: the Olmsted County study of urinary symptoms and health status. J Urol. 1999; **162**(4): 1301-6.
9. Kyprianou N, Tu H, Jacobs SC. Apoptotic versus proliferative activities in human benign prostatic hyperplasia. Hum Pathol. 1996; **27**(7): 668-75.
10. Ho CK, Habib FK. Estrogen and androgen signaling in the pathogenesis of BPH. Nat Rev Urol. 2011; **8**(1): 29-41.
11. Roberts RO, Bergstralh EJ, Cunningham JM, Hebbring SJ, Thibodeau SN, Lieber MM, et al. Androgen receptor gene polymorphisms and increased risk of urologic measures of benign prostatic hyperplasia. Am J Epidemiol. 2004; **159**(3): 269-76.
12. Timms BG, Hofkamp LE. Prostate development and growth in benign prostatic hyperplasia. Differentiation. 2011; **82**(4-5): 173-83.
13. Hammarsten J, Hogstedt B. Clinical, anthropometric, metabolic and insulin profile of men with fast annual growth rates of benign prostatic hyperplasia. Blood Press. 1999; **8**(1): 29-36.
14. Ozden C, Ozdal OL, Urgancioglu G, Koyuncu H, Gokkaya S, Memis A. The correlation between metabolic syndrome and prostatic growth in patients with benign prostatic hyperplasia. Eur Urol. 2007; **51**(1): 199-203; discussion 4-6.
15. Kohnen PW, Drach GW. Patterns of inflammation in prostatic hyperplasia: a histologic and bacteriologic study. J Urol. 1979; **121**(6): 755-60.
16. Nickel JC, Roehrborn CG, O'Leary M P, Bostwick DG, Somerville MC, Rittmaster RS. Examination of the relationship between symptoms of prostatitis and histological inflammation: baseline data from the REDUCE chemoprevention trial. J Urol. 2007; **178**(3 Pt 1): 896-900; discussion -1.
17. NICE. Management of lower urinary tract symptoms in men. National Institute of Clinical Excellence; 2010.
18. Neal DE, Ramsden PD, Sharples L, Smith A, Powell PH, Styles RA, et al. Outcome of elective prostatectomy. BMJ. 1989; **299**(6702): 762-7.
19. Griffiths D, Hofner K, van Mastrigt R, Rollema HJ, Spangberg A, Gleason D. Standardization of terminology of lower urinary tract function: pressure-flow studies of voiding, urethral resistance, and urethral obstruction. International Continence Society Subcommittee on Standardization of Terminology of Pressure-Flow Studies. Neurourol Urodyn. 1997; **16**(1): 1-18.