Benign prostatic hyperplasia

R J SIMPSON

SUMMARY

The clinical syndrome of benign prostatic hyperplasia reflects a complex interplay between benign prostatic enlargement, which will affect almost all men by the age of 80, and the resulting outlet obstruction and lower urinary tract symptoms. The disease is now known to adversely affect the quality of life of around one man in three over the age of 50. New medical treatments and new surgical interventions are challenging the previous standard treatment of transurethral resection of prostate, which continues to have a morbidity of 17% and some mortality. Primary care will be increasingly involved in shared care with particular emphasis on monitoring of patients on watchful waiting medical therapy and following operative intervention.

Keywords: prostate; benign hyperplasia.

Introduction

THIS review is based on a Medline search, together with additional articles cited in a previous review[1] and two recent texts.[2,3] Benign prostatic hyperplasia (BPH) will be reviewed here with only a passing reference to cancer of the prostate.

There is a major problem of terminology in considering this clinical area. Having changed the name from hypertrophy to hyperplasia, there is still much confusion created by new information over the past 20 years. New terms such as benign prostatic enlargement (BPE), used to describe the growth of the gland with ageing, lower urinary tract symptoms (LUTS), used to describe the symptoms, are currently 'in vogue'. Throughout this review BPH will be used to mean the clinical syndrome.

Anatomy

The entire gland is composed of smooth muscle stroma in white acini. McNeal, who dismissed the previous concept of 'lobes', described three anatomical zones: the peripheral zone, which comprises around two thirds of the gland; the transition zone, which comprises 10% of the gland in two symmetrical lobes alongside the prostatic urethra and is separated from the rest of the gland by the fibro-muscular stroma; and the central zone, one quarter of the volume of the gland, found mainly at the base of the prostate with the tissue surrounding the ejaculatory ducts.[4]

Pathology

The pathology of prostatic disease may be considered in three sections:

1. Prostatitis: inflammation or infection occurring as an isolated event mainly in younger men, though in more chronic or recurrent forms in older men.
2. BPH and prostatism: rarely occurring in men under the age of 40 years. BPH is nodular, found predominantly in the transition zone, but also in the peri-urethral area. Apart from the steadily increasing number of nodules there is also a diffuse enlargement of the transition zone, which accounts for a substantial proportion of the overall enlargement.
3. Cancer of the prostate: predominantly a condition of the elderly, and is not causally related to BPH, but these conditions frequently coexist.[5] The presence of overt or microscopic cancer, or predictors of cancer such as a prostatic-specific antigen results raised above expected age-related levels, can complicate the management of BPH.

R J Simpson, MBChB, DPM, FRCPsych, general practitioner, honourary professor of psychology, Forth Valley GP Research Group, University of Stirling.

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Epidemiology

Early population studies of BPH included those by Jensen[6] in Denmark, and Wattanabe[7] in Japan, both in 1986. Berry,[8] reporting on a series of five necropsy studies, showed hyperplasia to exist almost exclusively in glands greater than 20 gms in weight and in men over 30 years of age. Further evidence from the Baltimore Longitudinal Study of Ageing showed a good level of agreement with autopsy prevalence rates.[9] The first large community study, published by Garraway in 1991,[10] showed lower prevalence rates than the autopsy studies in men selected as having either urinary flow rates of below 15 ml/sec, or specific levels of LUTS, or both. A parallel study, done in Omstead County, USA, by the Mayo Clinic, showed similar levels to the Scottish Community Study.[11] Much higher levels of BPE were found in the second Stirling BPH study where no clinical thresholds were applied before measuring prostate size (Table 1), rising to 913 per 1000 (95% CI 798–1000) at age 70–79 years.[12] BPE is so frequent as to be considered as much a normal part of ageing as grey hair or wrinkles.

Symptoms and signs: BPE, LUTS, and urinary flow

Having established that BPE is almost universal in men over the age of 70 years, we must turn to the other symptoms and signs for the diagnostic criteria of the clinical syndrome BPH.

LUTS, commonly sought in evaluating the clinical condition, include hesitancy in the initiation of micturition, a weak force of stream, stopping and re-starting or interruption of the stream, and terminal dribbling. These symptoms are sometimes classified 'obstructive'. Symptoms of nocturia — frequency, urgency, dysuria and a sensation of incomplete voiding — represent 'irritative' symptoms. The evidence is poor for this pragmatic division; only urgency and urge incontinence correlate with the presence of a detrusor instability.[13] Abrams[14] has recently argued cogently that the term 'filling symptoms', for frequency nocturia urgency and urge incontinence, would be preferable to the term 'irritative' since the latter term implies some form of inflammation, and the term 'voiding symptoms', to include hesitancy, slow stream and intermittency, and a feeling of incomplete emptying, terminal dribbling and post micturition dribble, would be better than the term 'obstructive'.

Then there is the urinary flow measurement. The trace produced by a uroflow machine has to be read in a similar way to an electrocardiograph tracing rather than simply accepting the mathematical data. However, 'QMax' (maximal flow) is generally regarded as the most useful measure of flow.[15]

The presence of BPE, LUTS, and reduced uroflow in a variety of combinations, provide the basis for diagnosis of BPH. However, BPE, LUTS and uroflow do not have any significant

Table 1. Age-specific prevalence of BPH.

Age	Stirling[a]	Necropsy[b]	Baltimore[c]	Baltimore[d]	Stirling[e]	Mayo[f]
40–49	61.5	24	28	10	15	9
50–59	77.6	43	50	28	26	18
60–69	89.2	72	71	42	43	32
70–79	88.9	82	80	55	40	36

[a]Stirling BPH Natural History Group (clinically unselected CPA data); [b]Necropsy meta-analysis of five studies (Berry et al[8]); [c]Baltimore Longitudinal Study of Ageing; physical examination and hisotry (Guess et al[9]); [d]Baltimore Longitudinal Study of Ageing: digital rectal examination (Guess et al[9]); [e]Stirling BPH Natural History Group: phase one study (clinically selected) (Garraway et al[10]); [f]Mayo, Clinic data (Chute et al[11]).

relationship.[12,15,16] Part of the explanation for this lies in the variety of ways in which the gland enlarges, with predominant enlargement, particularly later in life, being in the transition zone.[17] BPH is not a simple condition where rigid threshold criteria can be easily applied to establish a diagnosis.

Difficulties for clinicians are increased by two further factors: failure of men to consult about either their symptoms or slow stream until the changes are advanced,[18] and lack of clarity about the natural history of BPH. The low level of knowledge about prostatic disease found in European men[19] may be improving. However, as symptoms and reduced flow are accepted as a normal part of ageing, only pain, haematuria and acute retention are perceived as reasons for seeking medical help.[20]

Natural history

Progression

The symptoms that patients do experience may not progress over time. Follow-up studies by Birkhoff[21] (1976) showed half the patients' conditions as unchanged or improved over a two-year period (n = 26). Ball,[22] in 1981, following up 127 men with prostatism for five years, found 97 had remained untreated. The Stirling BPH Natural History Group, following a larger sample over one[23] and three[24] years, showed that the overall prevalence of urinary symptoms increased. However, the condition of up to a quarter of the men who previously reported urgency and dribbling improved, while only one third reported deteriorated urinary symptoms. There was an overall increase of 19% in urinary peak flow, probably due to familiarization with the test.[25] This is known to occur especially in younger men.[26] There is a general decline in urinary flow with ageing[27] shown in normative age-related data sets.[28] A three-year follow-up of 224/256 (95%) men aged 40–79 years with BPE in the Stirling cohort showed the percentage of men reporting interference with one activity of daily living rising from 49% at baseline to 63% at year 3, and those reporting interference with three activities rising from 21% to 28%.[29]

Risk factors

Biochemical factors

Dihydrotestosterone plays a central role in the development of the prostate,[30] but the biochemical factors underlying enlargement associated with increasing age are unclear. Current thinking suggests that BPE may be due to an increasing imbalance between factors associated with cell growth and cell death. An understanding of the interplay between the various growth factors may lead to the development of newer and better medical treatment.[31]

Other risk factors

Guess summarized the published evidence with respect to racial, social and geographical variation in BPH as 'fragmentary, partly based on anecdotal reports and limited by a lack of structural diagnostic criteria and modes of case ascertainment'.[1] Moderate smoking may be associated with lower rates of prostatectomy,[32,33] however, this may be due as much to early death or unfitness for elective surgery in older men, as to any possible causal relationship with BPH.[34] Evidence for a relationship between BPH and cirrhosis,[35] and also diabetes mellitus,[36] is equivocal.[37]

Early reports[38,37] that BPH was more prevalent in those with higher educational backgrounds or social class were in studies flawed by highly selected populations. The Stirling Community Study found no social class variation.[18]

There may be an inverse association between alcohol consumption and eventual prostactectomy.[39]

Genetic factors appear to play some part as shown both in the study of twins[40] and case-control studies.[41]

Complications

Almost 30% of men who go on to have prostatectomy, present with acute urinary retention.[42,43] Birkoff[21] felt this presentation to be independent of the degree of prostatism (n = 26). In an East Anglian practice in 1969, Craigen[44] found symptom duration of <3 months in acute retention (n = 89). A follow-up of those who had not presented in this way (n = 129) found <10% developing acute retention over the next seven years. These findings were replicated by Powell[45] who found little evidence of symptoms warning of retention.

Bladder outflow obstruction (BOO) can lead to recurrent urinary tract infection (UTI) and pyelonephritis or chronic urinary retention, dilatation and hydronephrosis. Reporting on acute renal failure, Feast[46] noted an incidence of 172 million in adults, with 25% (n = 31/125) due to prostatic disease. For this prostate group the survival rate was 84% at three months. Chronic renal failure, where prostatic causation accounts for a lesser proportion (12%),[47] may be entirely preventable[48] through early detection by general practitioners.[49] Elevated urea/creatinine is associated with precipitant admission[42] and is more likely in the United Kingdom (UK) to result in transurethal resection of prostate (TURP) being undertaken by surgeons in training grades.[42] Such elevations are associated with more post-operative complications and mortality.[50-52]

Bladder stones were reported as a reason for prostatectomy in 1–2% of cases.[42,43, 53,54] Grosse,[55] in a large necropsy study (n = 19 863), found the prevalence of stones in men over the age of 60 at a rate eight times higher in those with BPE (3.4%) than either non-BPE men (0.4%) or women (0.3%).

Current pathways to diagnosis/tests

Shared care of BPH is still in its infancy, although clinicians generally favour this approach.[56] By 1995 in the UK, 62% of urolo-

gy centres operated a prostate-specific clinic, allowing efficient 'fast tracking' of severe cases. An increasing number of these clinics are being run by nurse practitioners, however, management decisions are still determined by consultants, with true sharing with primary care still to be developed. Almost three quarters of the remaining 38% of urology centres, with traditional urological outpatient services, wished to change to a prostate-specific clinic.[57]

The UK British Prostate Group[58], the WHO-sponsored International Consensus Committee (ICC),[59] and the American Guidelines Group[43] concur that mandatory investigations should include:

- full medical history,
- urinary symptom review,
- digital rectal examination (DRE),
- urine analysis, and
- serum creatinine.

In the UK these can readily be carried out in primary care.

There is less agreement about other tests, such as:

- Prostatic Specific Antigen (PSA): if suspicion of cancer or positive family history of prostatic cancer in men aged <75 is noted,
- uroflometry: currently assessed in only 40% of UK prostatectomy patients,[42]
- residual urine (RU): despite wide variation in individual patients,[60] RU is used as an indication for surgery,[61] though it may reflect bladder dysfunction rather than obstruction,[62] and
- pressure flow studies: arguably helpful in predicting poorer outcomes from operation, by establishing detrusor hypotonicity.[63,64]

Uroflowmetry

Since Renfish's first attempts at measuring urinary flow in 1897,[65] simple, increasingly cheap, effective and consistent mechanisms have been developed.[66] Normative data combining ageing, voided volume and uroflow have been attempted,[28,67] but their value is questionable.[68] The QMax, a key indicator,[69] is not sufficient to diagnose BOO. Uroflow, which is the product of bladder contractions and urethral capacity, can be affected by stricture and by abdominal straining as well as psychological stress.[70] Variations within individuals of 4.1 ml/sec or more have been observed and, for this reason, paired readings may be valuable.[71] Regression to the mean, found in repeated measures in a cohort selected originally for low QMax, emphasizes the dangers of isolated uroflow readings in diagnosing BPH.[72] Despite these caveats, it would appear that QMax readings of >20 ml/sec are unlikely to be associated with BPE of >40 gm.[8]

Symptom scores

Barry[73] underlined the benefits of using validated instruments such as the American Urological Association (AUA) Symptom Index[74] and the International Prostate Symptom Score (I-PSS) Symptom Index, which has an additional specific 'quality of life' question and is widely used in Europe. The earlier Boyarsky Index[75] was developed for evaluative rather than predictive purposes, whereas the Madsen-Iversen Index[76] was designed to aid selection of patients for surgical intervention. It is important to recognize at the outset that higher scores on many of these symptom indices do not diagnose BPH, nor even distinguish adequately between BOO, bladder neck or urethral stricture.[77] Indeed, such scores may be achieved by women![78] The increasing recognition of the importance of the effect upon the patient's quality of life of LUTS has been recognized in the US by the introduction of a questionnaire on troublesomeness.[79] This Symptom Problem Index has four questions asking:

1. How much physical discomfort did the urinary problems cause?
2. How much worry did the patient have because of urinary problems?
3. How bothersome was urination over the past month?
4. How much time had the problems kept the patient from doing the kind of things they would usually do?

Treatment

Surgical: TURP

The main intervention for the treatment of BPH is still TURP.[80,81] So common is this operation, that a probability of prostatectomy occurring in the lifetime of a 40-year-old in the US has been calculated as 29%.[34] The main benefit of TURP is towards obstructive symptoms, but irritative symptoms may also improve where bladder preoperative changes are not prolonged or excessive.

Indications

The UK National Prostatectomy Audit[42] found that 62% of men (3326/5361) had at least one strong indication[61] for operation. These were:

- Acute retention; n = 1507 (28.1%),
- chronic retention (residual urine volume of >196 ml); n = 1403 (26.2%),
- elevated creatinine/urea; n = 826 (15.4%),
- suspected malignancy; n = 725 (13.5%),
- haematuria; n = 392 (7.3%), and
- bladder stones; n = 91 (1.7%).

Although the remaining 38% (2035) had none of the above indications for operation, 1531 of these men did complete an AUA symptom score. This indicated mild symptoms in 55 men (3.6%); moderate symptoms in 591 (38.6%) and severe symptoms in 885 (57.8%). In the US, in marked contrast to the UK, the overwhelming majority of TURPs are undertaken for symptoms only.[82] Mortality and morbidity comparisons between the US and UK should, therefore, be treated cautiously. However, in both countries TURP is being undertaken on men who have a significant level of co-morbidity in up to 75% of cases.[42,52,53] The rate of complications is around 17%,[52-54] and is not significantly different for those with co-morbidity, nor does the rate increase with ageing in those below 80 years.[42]

Mortality and morbidity

Average mortality at all ages occurring within a month of the operation has improved significantly in the US from 2.5% in 1962 (n = 2015)[50] to 1.3% in 1974 (n = 2223)[51] and 0.23% in 1989 (n = 3885).[52] In the UK, recent reports indicate levels of below 1% (n = 388, n = 1400).[53,54] However, higher rates occur in older men,[52-54] especially those aged over 80 years, in operations where malignancy is present[53] and in sites where less than 100 operations per annum were undertaken.[54] Some studies have suggested that the longer-term mortality from TURP is worse than open prostatectomy,[83] however, Fugslig[84] found no greater mortality than that of the background population in a 10-year follow-up.

Morbidity appears to be associated with longer operating times (>90 minutes), larger gland size (> 45 g), and acute urinary retention.[52] Immediate complications include:

- Bleeding, with or without clot retention, with patients reporting higher rates (15%) than surgeons (11%),[53]
- failure to void,
- UTI,
- TURP syndrome (hypovolaemia from absorption of irrigant solution),
- myocardial arrhythmia, and
- indwelling catheters (2.4% of Mebust's sample in 1989[52]).

Longer-term problems include retrograde ejaculation in a majority of men.[85,52,54] Thorpe[86] reported no verifiable evidence of pre-operative sexual counselling in 70% of men (977/1396). A worsening in the quality of sex life has been reported in up to 25% of men.[87,53]

Roos,[84] reviewing 12 090 Canadians, 36 703 Danish and 5284 English procedures, found a re-operative rate of 12–15%.[42] Stress (2.9%), urge (1.9%), or total incontinence (1%) is another important outcome.[43] Urethral stricture or bladder neck obstruction may occur in between 3%[42] and 16% of cases.[88]

Outcome studies concur that greatest improvement in symptoms and quality of life is found in patients who had severe symptoms pre-operatively, with >90% reporting satisfaction compared to <80% for patients with moderate symptoms, and even lower levels for those with mild symptoms.[89,52,53,84] Although flow rates of >15 ml/sec may predict a poorer outcome,[90] other maximum flow rates do not predict the outcome of prostatectomy.[91,63]

Alternative surgical treatment

Many alternative procedures have been tried, including transurethral incision of prostate (TUIP), which is less likely to produce retrograde ejaculation and may have lower morbidity rates but higher re-operative rates (up to 20% at 10 years).[92] Balloon dilatation is less invasive, but has significant recurrence rates.[93.94] Laser ablation treatments (resection and vaporization) seem promising in reducing the length of stay in hospital, with an improvement in flow rate and symptoms intermediate between TURP and medical therapy.[95] Thermotherapy is being evaluated.[96] Urinary stenting is a quick procedure, carried out under local anaesthetic, with immediate, if temporary, relief.[97] There is a need for careful, controlled trials of these methods before they are widely adopted.

Medical treatment

There are three classes of medical treatment currently in use: alphablockers and 5-alpha reductase inhibitors, which have proven benefit, and phytotherapy, which is equivocal. All three medical treatments have been found to have substantial placebo effects in randomized controlled trials.

Alpha 1-adrenoreceptors are found both in the prostate smooth muscle and the base of the bladder. Blockade, with successful alleviation of symptoms, was first reported using phenoxybenzamine by Caine in 1984.[98] Subsequent research has proved that selective alpha blockers prazosin,[99] indoramin,[100] alfuzosin,[101] terazosin,[102] and doxazosin are safe and effective but have numerous, mainly cardiovascular, side-effects. Doxazosin and terazosin, taken once daily, are more expensive, as is alfuzosin. Concerns that the effect of alpha blockers may not be sustained in the long term[99] have been ameliorated by reports of efficacy (40–59% showing at least 30% improvement in QMax and safety of terazosin in a 42-month follow-up[103]).

The 5-alpha reductase inhibitor, finasteride, produces a reduction in prostate size (up to 28%[104]) after 3–6 months, with an improvement in symptom score and increased uroflow found in at least 50% of men. Safety and efficacy on 3-year follow-up data showed good tolerance and sustained benefit;[105] it is most effective in men with larger prostates.[106] The side effects of finasteride are few (impotence 3.7%, decreased libido 3.3%, decreased ejaculation).[107] With finasteride treatment, PSA values are halved at all levels and ages, and therefore, readings on treatment should be doubled to obtain the standard clinical measure.[108]

Phytotherapy, pollen or plant extract is widely used by self-prescription. The limited trial work has yet to be replicated to establish efficacy, though cernilton has shown some benefit.[109]

Prostatic cancer treatments including castration and hormonal treatments cause involution of the gland but are unacceptable for BPH alone. Current research into growth factors and proto-oncogenes responsible for cell death, may hold longer-term promise for both BPH and cancer.[110]

Watchful waiting (WW)

Wasson[111] reported on a comparison of WW versus TURP for moderate symptoms (AUA score 10–20), excluding men with hard indications for TURP. There were 27/249 treatment failures in the surgery group and 47/276 in the WW group (relative risk = 0.48; 95% CI = 0.3–0.77). The conclusion is that WW is a safe option. Barry[112] has concluded that patient preferences should be the dominant factor[113] in the US, where the use of interactive video in assisting decision making seems beneficial.[114] There is at present insufficient evidence upon which to base guidelines as to the frequency of review as part of a watchful waiting management plan.

Conclusions

BPH is an underdiagnosed condition that significantly affects the quality of life of many men and should be part of opportunistic health promotion in men aged over 50. Diagnosis is not a simple matter of threshold symptom scores, nor reduced urinary flow, nor BPE. The natural history remains unclear. A multifactorial approach to diagnosis is required with patients playing a large part in treatment choice. Where absolute indications for surgery are present, or severe bothersome symptoms, TURP remains the treatment of choice, but has significant morbidity and needs to have managed, long-term follow-up to prevent recurrence. New surgical treatments may prove valuable but need further evaluation. Medical treatments or watchful waiting in those men with moderate symptoms are acceptable options.

The coexistence of prostatic cancer is a problem in the continuing care of patients with BPH, and complicates the shift from secondary to primary care of diagnosis and management. True-shared care is likely to develop as the hospital prostate assessment clinics become as overburdened as the urology clinics they have superceded. Management of BPH will continue to require the skills of medicine as an art for some time, as much as an evidence-based approach.

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Address for correspondence

Professor R J Simpson, Forth Valley GP Research Group, Psychology Department, University of Stirling, Stirling, FK9 4LA.