The overactive bladder

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Introduction

The term ‘overactive bladder’ has been used sporadically for many years; according to the original definition of the ICS, the overactive bladder refers to the storage phase of the bladder and is diagnosed by urodynamics [1]. The overactivity is caused by involuntary detrusor muscle contractions that occur while the patient is trying to inhibit voiding. If caused by a neurological disease the overactive bladder was referred to as hyper-reflexic, and if by a non-neurogenic or unknown cause, as unstable. A different terminology will probably be proposed in the near future as it has become clear that the current nomenclature is unsuitable for many patients and does not correspond with the clinical reality [2]. Abrams and Wein [2] suggested the following definition: ‘the overactive bladder is a medical condition referring to the symptoms of frequency and urgency, with or without urge incontinence, when appearing in the absence of local pathology or metabolic factors that would account for these symptoms’. Incontinence is not a necessary condition for diagnosis, because about half of those with an overactive bladder are not incontinent.

This proposal starts from a very different perspective from the original definition: it would seem to accept that the involuntary bladder contractions can be symptomatic or not, the symptomatic form being termed overactivity. This is common knowledge to many physicians involved in urodynamic studies. For the overactive bladder to be symptomatic, an overactivity of the bladder muscle must occur at volumes below the patient’s functional bladder capacity and should occur under circumstances of normal daily activity. Moreover, the proposal accepts that the involuntary detrusor contractions should be felt by the patient. The exact relationship between the sensation of urgency and muscle activity of the bladder is not clear. There is some doubt about the relationship of urgency and detrusor pressure increase, because many patients with complaints of urgency do not have motor overactivity. Turner-Warwick once called unstable detrusor contractions a ‘variant of normality’ and this might be the case in some patients [3]. Thus there seems currently to be a transitional period of developing a definition of what is generally to be accepted as a true overactive bladder. However, whatever definition is finally adopted, symptomatic bladder overactivity is a very bothersome problem that can significantly reduce the quality of life of affected individuals.

Current aetiological concepts

Ideas for the cause of the overactive bladder are based on increasing knowledge about lower urinary tract physiology. There is ample evidence that micturition and bladder filling are independently organized in the brain: the pontine micturition centre and the pontine storage centre (PSC) in the cat do not seem to be interconnected at the level of the brainstem [4]. The group of neurones in the pons involved in the storage of urine is known as the PSC group or l-region, and projects to the motor neurones of the urethral sphincter in the nucleus of Onuf [5]. Bilateral lesions in the PSC cause an inability to store urine; bladder capacity is reduced and urine is expelled prematurely by excessive detrusor activity, accompanied by urethral relaxation. There is also a PSC in humans [6]. Most of the time bladder control is modulated in an inhibitory fashion by the diencephalic and cerebral cortex functions, the cerebral cortex being responsible for the timing of the control. Neurological deficits in these regions are known to be possible causes of bladder overactivity [7]. Lesions between the pontine and sacral micturition centre may cause neurological detrusor overactivity. Pathological afferent pathways might be important, as shown by the beneficial effect of electrical stimulation on these nerves in inhibiting detrusor function [8].

Abnormalities of bladder smooth muscle have been related to the occurrence of bladder overactivity. Prolonged obstruction could have an influence through structural deformation of the bladder smooth muscle, an increased production of nerve growth factor and induced neuronal enlargement [9]. Urethral resistance in women with an overactive bladder was much higher than that in women with no abnormality on urodynamic studies [10]. However, obstruction could lead to partial denervation, inducing denervation supersensitivity [11]; it could also
have metabolic effects through the generation of free radicals and lipid peroxidases [12].

Little has been published so far on a possible dysfunction in the sensory nervous system, although clinical data are in favour of such a cause of overactivity [13]. The possible role of urinary potassium on bladder overactivity through the A-delta and C-fibres corresponds with a similar pathogenesis [14].

Symptomatology of the overactive bladder
The clinical relationship between incontinence and the overactive bladder can be very variable. In patients with bladder overactivity there may be several groups with a different clinical picture, i.e. with frequency and urgency, with frequency, urgency and urge incontinence, with mixed incontinence (stress and urge), or with no apparent symptoms, where motor overactivity is discovered during urodynamic investigations undertaken for another reason. This last group probably needs no further diagnosis or treatment if the bladder contractions are really asymptomatic and unrelated to what caused the patients to initially consult their physician.

Epidemiology of the overactive bladder
Prevalence studies of the overactive bladder differ widely in the methods applied, survey populations and results; there is no conformity in their definition of the symptomatology, survey methods and validation. The prevalence of the overactive bladder has also probably been underestimated because many studies have been limited to patients with incontinence. This overlooks many people, mostly men, who are significantly troubled by frequency and urgency as a consequence of an overactive bladder. The condition is probably more common in women than in men. The results of a Gallup study in six European countries give an overall incidence of 17% of adults having one or more symptoms of an overactive bladder. That survey also showed that the incidence consistently increased with advancing age [2].

Diagnostic assessment of the overactive bladder
From the definitions given above it can be assumed that a detailed history is the key to diagnosing bladder overactivity in most cases. Frequency, urgency and urge incontinence alone or in combination form the basic group of symptoms of possible bladder overactivity. Anatomical, neurological and infectious causes should be excluded first, with a preliminary clinical examination and urine analysis. Primary-care physicians and many urologists will probably proceed no further with a diagnostic evaluation if these tests reveal no obvious pathology, but will initiate some form of treatment.

Urodynamic tests are needed when the probable diagnosis is unclear, if a neuropathy is suspected or if therapy has been unsuccessful. Conventional laboratory urodynamics failed to detect any abnormality in > 35% of patients in the study by van Waalwijk van Doorn [15]. Ambulatory urodynamic monitoring would seem to be better than conventional filling cystometry, as motor overactivity of the detrusor is more frequently detected [16]. However, again it would seem appropriate to accept that only if pressure rises correspond with the signs and symptoms do they have any diagnostic value for the overactive bladder, as changes in detrusor pressure can also be detected in many asymptomatic subjects [17].

Overactive bladder and quality of life
An overactive bladder has a detrimental effect on quality of life; in most domains (physical functioning, social functioning, vitality, role limitations) affected patients score significantly worse than do age-matched controls. Compared with the quality of life of patients with diabetes, hypertension and depression, only depression has a greater effect [18].

Treatment
The medical management of the overactive bladder has been a major concern for those involved in treatment during the last few decades. Several different aspects have been studied and methods of treatment evaluated; these are behavioural therapy, pelvic floor therapy, muscarinic receptor antagonists and other drugs, and intravesical treatment.

Behavioural therapy is one of the best single-treatment options as it has no risk and gives very acceptable results. The therapy should start with education and an explanation of normal lower urinary tract function, and the dynamic and clinical aspects of overactivity. When the patient understands what actually happens, he/she can better interpret the signs and symptoms after unstable bladder contractions. More information can be obtained from voiding charts and diaries; by completing these and by discussing them, the symptoms can be related to daily living.

When this knowledge has been acquired, training can start with timed voiding and bladder training regimens ('bladder drill'). This includes training to perceive the early signs of an overactive contraction (the 'warning'), urge inhibition, delayed voiding and reinforcement of these steps when successful. Fluid management is another important part of managing overactivity. A voiding diary is often the basis for evaluating and
setting goals, aiming for a better control of the bladder with a reasonable voiding interval and no incontinence. Training for good micturition habits can be useful. Behavioural therapy can be combined with other forms of treatment, e.g. drugs and pelvic floor exercises. This also facilitates the treatment of patients with mixed incontinence, a functional problem or pelvic floor disorders. Reassurance of the patient is always helpful and specific psychological help might be needed in some cases [19]. Behavioural therapy is effective, with published success rates of >50%, although the long-term results seem to be lower [20]. Most clinicians would agree that every patient with bladder overactivity should be provided with at least the basics of behavioural therapy.

**Pelvic floor physiotherapy** consists of several different techniques applied to treat the overactive bladder. Pelvic floor muscle exercises have been used to try to stop the developing autonomic contractions by squeezing the pelvic floor muscles. To date, published data do not allow a firm conclusion that this method is clinically successful, especially in the long term, although theoretically the method should work. Contraction of the pelvic floor muscles, electrically stimulated or voluntary, provides reflex inhibition of the detrusor muscle [21,22]; this provides the rationale to further explore its therapeutic value.

**Electrical stimulation** is an effective and well-tolerated treatment for the overactive bladder; it is considered to be a neuromodulating therapy which affects the neural signalling that controls continence. There is also an effect in striated muscles, causing hypertrophy of the muscles by recruiting fast-twitch fibres which would not be affected by exercise alone. Studies show that the use of vaginal electrical stimulators can reduce the occurrence of symptoms of an overactive bladder in about half of the patients treated [23]. However, the objective findings do not seem to correlate well with the subjective improvement.

**Biofeedback** is a type of learning or re-education which helps to retrain the patient. Information about one or more of the patient’s physiological processes is presented to the patient as a visual, auditory or tactile signal. For bladder overactivity, biofeedback has been used to relate immediately the changes in intravesical pressure (bladder or cystometric biofeedback) and as a method of pelvic floor training. As with all training programmes, biofeedback needs considerable effort from the patient and the training physiotherapist; patients also need to be well motivated and intelligent enough to understand what is expected of them. Those who guide the training must be motivated, skilful and maintain good contact with the patients. Biofeedback has few side-effects and can be used as an adjunct with other forms of treatment.

The original technique for biofeedback in managing idiopathic detrusor instability was described in 1978 [24]. Bladder biofeedback gave very acceptable results in two studies by the present author, one in adults and one in children [25,26]. As patients are able to visualise directly the development of intravesical pressure during bladder filling, they can learn to feel the sensory signals that accompany the unstable contractions, and can thus try to stop them with active contractions of the sphincter and pelvic floor. We noted that the problem could be controlled more effectively but that the unstable contractions continued in most of those treated with this technique. This could explain why some patients who were initially cured relapsed in the long term, but the training can be repeated successfully. Cystometric biofeedback is invasive and should therefore be used mostly in refractory cases. Complications such as urinary infection are very rare.

**Pelvic floor biofeedback** has been assessed by several groups, with variable results; the technique has the best chance of success as part of a comprehensive treatment programme [27]. Such biofeedback can use the electromyographic activity of the urethral or anal sphincter or of the pelvic floor; it can also be used to follow pressure changes in the anal canal or in the vagina, measured through balloon catheters. Published results are few and not always easy to interpret because of a possible bias in patient selection, variations in methodology or in the combinations of treatment given. There is a need for randomized controlled trials to determine its optimum place in treatment programmes. The technique causes almost no complications or side-effects.

**Muscarinic receptor antagonists**

These drugs still form the mainstay of treatment for the overactive bladder and there is ample clinical evidence that they are effective. However, the side-effects limit their use, especially those of dry mouth, constipation and blurred vision. Oxybutynin has been used for many years and has good clinical efficacy [28]. To limit its side-effects, alternative routes of administration have been used [29]; extended-release oral formulations and stimulation of salivation were assessed to improve this bothersome symptom. There have been advances in the understanding of muscarinic receptors and bladder function which have lead to the search for tissue- or subtype-selective antimuscarinic agents with improved tolerability. Tolterodine and darifenacin are being increasingly used in clinical practice; the side-effects from these drugs appear to be less and the drugs more specific [30,31]. Several questions remain, e.g. about the effect of long-term treatment, and whether adaptation occurs after
prolonged periods of use, so that drugs might need to be changed at regular intervals.

**Other drugs**

Imipramine, duloxetine, drugs affecting noradrenaline, dopamine or γ—aminobutyric acid receptors, and α1-adrenoceptor antagonists, have all been assessed, with some success. Potassium-channel openers, prosta-glandins, selective or nonselective inhibitors of cyclooxygenase, and drugs that reduce afferent activity are possible ways of pharmacological treatment that have been explored.

**Intravesical treatment** has attracted some interest; this route of administration tends to reduce the parasympathetic efferent activity or to cause de-afferentiation of the bladder. Intravesical oxybutynin has been used mainly in patients with a neuropathic bladder who also use intermittent self-catheterization [29]. Capsaicin and resiniferatoxin are under study [32]. The injection of botulin toxin into the detrusor muscle to treat bladder hyper-reflexia has been assessed in patients with neurological bladder overactivity and seems to give promising results [33].

Thus the medical management of the overactive bladder is constantly developing; however, for several other methods a proper evaluation is not yet possible because there are few controlled studies, but their use can still be advocated as most have no side-effects, are harmless and based on plausible hypotheses. The best approach is to initiate the treatment of idiopathic bladder overactivity with behavioural training, physiotherapy and drugs.

**Surgical management**

Denervation techniques were popular for some time but have been gradually abandoned. Bladder transection by open surgery, endoscopic or transvesical phenolization, hyperbaric bladder distension and peripheral denervation of the bladder provided promising early results but the long-term outcome was poor. Currently sacral de-afferentation by dorsal root rhizotomy of S2–S5 is successful in patients with a complete supraspinal cord lesion [34].

Sacral neuromodulation has become popular, probably because it bridges the gap between conservative treatment and highly invasive options. Sacral neuromodulation comprises three main stages; the percutaneous location of the sacral spinal nerves with a needle electrode, percutaneous test stimulation with wire electrodes to assess the therapeutic potential in each patient over a period of a few days, and implantation of a stimulation system if the second stage was successful.

At present there are no clinical variables that can reliably predict the efficacy of neuromodulation in an individual patient. All patients must have a test stimulation before having an implant, but success with the test does not always mean certain success with the implant. Some centres report a close match between those responding in the subchronic and chronic effects of sacral neuromodulation; in contrast, others report therapeutic failure rates in up to half of patients during chronic sacral neuromodulation, despite good responses to the shorter test trials.

Several clinical studies reported significant therapeutic success for neuromodulation in patients with bladder overactivity, especially if detrusor overactivity could be detected [35,36]. The complication rate for neuromodulation is low, but the technique is expensive and should preferably be offered to those with symptoms refractory to conservative treatment. There are arguments that the stimulation operates through the afferent nerves [37] but the exact mode of action remains to be elucidated.

**Bladder augmentation**

Gastrointestinal segments are commonly used for bladder replacement and augmentation. These techniques are needed infrequently in patients with an overactive bladder but the rare refractory patient with substantial symptoms may benefit from them. However, contact between gastrointestinal tissue and urine can induce several complications. Autoaugmentation has been successful in several series and many new techniques are being developed after experimental assessment and will soon appear in clinical practice if the clinical results are good. De-epithelialized bowel segments have been used and a system of progressive dilatation for ureters and bladders described. There is a new interest in the use of acellular collagen-based matrices as scaffolds for bladder regeneration. Recently, bladder tissue has been engineered using selective cell transplantation techniques, such that the tissue can be used in children and adults. Tissue is taken from the host, the cells are dissociated and expanded in vitro, re-attached to a matrix and implanted in the same host. The prospects are good but the results of the clinical applications are awaited [38].

**Summary**

The overactive bladder causes frequency, urgency and/or urge incontinence, and may have a significant effect on quality of life. The definition of the overactive bladder needs clarification and this should help to overcome the current confusion. Possible neurological, muscular and metabolic causes have been proposed but in many cases
the exact cause remains unclear. The diagnosis depends greatly on a detailed history, clinical examination and urine analysis. Urodynamic investigations are indicated when neuropathy is suspected, the treatment remains unsuccessful or if there is doubt about the exact situation. The overactive bladder can be treated conservatively, by training, physiotherapy and drugs. For refractory cases neuromodulation, denervation techniques and bladder augmentation may be indicated.

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