Sympathetic nervous system and dysfunction of the lower urinary tract

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Summary

Careful clinical and investigative protocols allow the identification of a homogeneous group of patients with prostatodynia or ‘anxious bladder syndrome’ (underactive detrusor function). Psychophysiological studies and urodynamic measurements in such patients demonstrate remarkably consistent results, which, whilst lending support to the hypothesis that the sympathetic nervous system may affect bladder and urethral function, do not offer objective proof that adrenergic mechanisms are directly responsible for the observed dysfunctional state.

Key words: male outflow obstruction, prostatodynia, psychophysiology, sympathetic nervous system.

Introduction

The role of the sympathetic nervous system in both normal and abnormal function of the lower urogenital tract remains unclear. Although certain pharmacological and histochemical observations suggest an importance for adrenergic mechanisms, and this will particularly apply to genital as opposed to urological function, it remains difficult to correlate fluctuations or changes in central sympathetic nervous activity with recordable and reproducible effects on target tissue. It is superficially attractive, for example, to explain the ‘continent state’ in terms of increased adrenergic tone, which at once increases relaxation of the bladder dome (β effect) and constricts the musculature of the outflow tract (α effect). However, detailed histochemical studies underline the difficulty in identifying noradrenergic staining material within the detrusor muscle and for these and other reasons it would seem improbable (at least in the human) that such mechanisms play a crucial or central role in the storage phase of the micturition cycle.

Apart from its undetermined role in the physiological control of the normal lower urinary tract, it is possible to consider whether the sympathetic nervous system plays any part in the genesis of the various dysfunctions which may affect bladder or urethral function in patients without evidence of neurological abnormality. Clinical studies on cases of prostatic outflow tract obstruction, bladder neck obstruction, bladder instability, reflux uropathy etc. do not reveal consistent changes which may be confidently related to altered adrenergic tone, be this enhanced or diminished. There are, however, two inter-related conditions which on careful investigation are found to be associated with at least some of the known systemic effects of sympathetic overactivity. These conditions are prostatodynia and the ‘anxious bladder syndrome’, and a critical examination of the history and urodynamic findings in such patients might allow a judgment to be formed as to whether inappropriate sympathetic activity plays any part in the pathogenesis and maintenance of these dysfunctional states.

Clinical features

Prostatodynia is a diagnosis of exclusion which can only be reached after exhaustive tests have ruled out all other possible causes for the patient’s symptom complex. A full history and examination will of necessity be followed by urography, urodynamic studies and cystoscopy with biopsy in order to identify any pathological disease process. The term itself was coined by Drach et al. [1] in an attempt to resolve the confusing nomenclature surrounding those patients whose persistent symptoms were associated with a negative investigative screen and whose expressed prostatic secretion was sterile on culture and contained few (<10 per high-power field) leucocytes on direct microscopy. The phrase
(meaning prostatic pain) has been criticized in some circles, as the source of the pain remains obscure, but it can be recommended on the grounds that it has the attraction of descriptive accuracy and avoids the confusion caused by the various names previously applied to these patient groups (prostatosis, pelvic floor tension myalgia etc. [2]).

Although prostatodynia may occur throughout adult life, most patients are between the ages of 30 and 60 years. The diagnosis is made easier in younger patients by the absence of symptom complexes associated with prostatic hypertrophy. The major symptom is that of pain, which is described as being located behind the scrotum in the centre of the perineum. The pain varies from a mild ache to a dull boring discomfort and may be present for many years, although the symptoms commonly vary as time passes. The pain may be exacerbated by ejaculation and associated discomfort may be experienced in the suprapubic area, testes, epididymes and loins [3].

Symptoms of voiding disturbances have been recorded by several authors and are often attributed to obstructive dysfunction at the bladder neck, although some workers dispute this interpretation [4]. Peak urine flow rates are known to be reduced in patients with prostatitis [5] and are similarly reduced in patients with prostatodynia although, as the flow rate is commonly greater than 10 ml/s, few patients make a primary complaint of poor stream [4]. Day-time frequency and nocturia are variable symptoms which require objective confirmation by means of frequency-volume charts (Table 1).

Occasionally patients are seen whose symptoms closely resemble those of prostatodynia but whose disorder appears to be related to a more generalized psychological disturbance. The nature of the complaint and the personality of these patients has lead them to be described as having an 'anxious bladder syndrome' [6]. The majority of these patients present before the age of 45 years and commonly lead a stressful 'executive' lifestyle. The urological symptoms often exhibit a periodicity similar to that recorded in cases of duodenal ulceration, and indeed dyspeptic disease has been observed to occur in these patients approximately twice as often as might be expected from a study of normal controls. Such observations lend weight to theories suggesting a psychological cause for the symptom complex.

Frequency of micturition is often severe by day but unusual at night. Marked perineal discomfort as described by patients with prostatodynia is unusual. Severe hesitancy is a common complaint and leads in some cases to a characteristic inability to micturate in the presence of other people, such as in a public toilet. This extraordinary symptom is very typical of the anxious bladder syndrome. Suprapubic bladder pain, worse if the bladder becomes overfull, loin ache and minor initial dysuria, are described by some patients. The urine flow is commonly intermittent in nature and the patients may push to speed emptying of the bladder.

Although the apparent multi-system nature of this disorder lends credence to arguments suggesting the importance of psychological factors it will not be forgotten that organic lower urinary tract disease may give rise to considerable anxiety, and thus urodynamic studies will be essential to exclude such conditions as bladder neck obstruction, which also give rise to slow stream in younger men.

Post-micturition dribble is a common symptom described by patients with either prostatodynia or anxious bladder. Video cystometric tests in these patients have demonstrated that urine within the prostatic urethra becomes 'trapped' by premature closure of the bladder neck at the termination of voiding and this small amount of urine leaks out distally after the completion of micturition.

**Psychophysiological studies in prostatodynia**

In most patients the genesis of the prostatodynia symptom complex remains unknown. Several authors have commented on the tendency for such patients to have a tense and neurotic personality [2, 7]. Anxiety, depression and hypochondria, reported on the basis of personality questionnaires, were the most common psychological abnormalities discovered in patients with non-inflammatory prostatitis [8]. This form of analysis can be extended to

<table>
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<tr>
<th>Table 1. Symptoms in 37 male patients with prostatodynia</th>
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<tr>
<td><strong>Somatic symptoms</strong></td>
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<tr>
<td>Perineal pain</td>
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<td>Pain after ejaculation</td>
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<tr>
<td>Suprapubic discomfort</td>
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<td>Penile pain</td>
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<td>Testicular pain/aches</td>
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<td>Loin pain</td>
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(76%) (56%) (55%) (44%) (35%) (17%)
include psychophysiological techniques which attempt to relate behavioural aspects of affective and cognitive processes to objective measures obtained under controlled laboratory conditions. Similar techniques have been employed in conditions such as depression, anxiety, schizophrenia and psychosomatic disorders [9].

The most common psychophysiological test procedures are designed to assess the reactivity of the autonomic nervous system. Measures of palmar skin conductance and sweating correlate strongly with skin-related sympathetic nervous activity [10]. Additional information may be obtained from cardiovascular variables such as heart rate and finger pulse volume as well as from somatic measures such as the frontalis electromyogram. The response of these functions to an altered state of emotion may be readily observed and it has proved possible to differentiate normal and neurotic groups by means of various estimates of psychophysiological arousal including basal activity, response amplitude and the time taken for psychological recovery after an experimental stressor, which may be physical (e.g. cold pressor tests) or cognitive (e.g. mental arithmetic).

Two psychophysiological studies on patients with prostatodynia have been reported [11]. In one experiment a group of subjects with prostatodynia was compared with a control group of healthy subjects and, in a second, patients with prostatodynia were compared with a further group of 16 patients with bacterial prostatitis. In all these patients the diagnosis of prostatodynia had been thoroughly verified by clinical, bacterial and urodynamic means.

A symptom distress check list (SCL-90) was used to assess neurotic symptomatology [12]. This is a 90 item self-report questionnaire that assesses a broad range of symptoms commonly reported by psychiatric out-patients. The psychophysiological measures to be recorded were respiration rate, forehead electromyogram (EMG), heart rate, palmar skin conductance or sweating. In the second experiment only heart rate and forehead EMG were recorded. The laboratory assessment involved a 10 min adaptation period after electrode attachment, after which a series of taxing procedures (2 min) were performed, including mental arithmetic, white noise (90 dB intensity), two memory tests, a word recognition test and a reaction time test. Each test was preceded and followed by a 2 min base line adjustment period. The psychophysiological data were analysed as mean values for each of the 2 min duration session phase. Each function was measured to determine if there was a significant overall difference between groups and whether they reacted differently within the session. The statistical test was the analysis of variance with repeated measures. Each sub-scale of the SCL-90 was analysed separately by using independent t-tests.

Patients with prostatodynia were found to have a significantly higher mean heart rate than controls ($P = 0.007$) and there was additionally evidence of elevated frontalis muscle tension, although the difference fell short of statistical significance, because of between-group variability and the small number of normal control subjects. Mean muscle tension levels within the prostatodynia patients was similar to those previously obtained from patients with an anxiety state who had been assessed by the same procedure [13]. Respiration rate effects also differed between the two groups. Control subjects showed an overall decline in respiration rate at the end of the stressor situation, which was not seen in patients with prostatodynia, and this reduction was an example of the different recovery rates in normal and neurotic groups after exposure to stressors. Palmar skin conductance levels did not differ between the two groups.

The prostatodynia patients had a higher overall level of neurotic symptomatology on the SCL-90 with significantly higher ($P = 0.04$) scores on the dimension of 'somatic anxiety', which contains 12 items relating to complaints of physical pain and discomfort. Scores of dimensions of depression, general anxiety and hostility were elevated in the patient group but not of statistical significance. It should be noted that although the dimension of 'somatic anxiety' is made up of questions concerning physical pain it does not contain symptoms specifically associated with the lower urinary tract.

In the second experiment the symptom distress check list scores for prostatodynia patients were generally higher than those of the bacterial prostatitis group (Fig. 1). Again the highest mean score for the prostatodynia group was on the somatic anxiety scale, and these were significantly different ($P = 0.05$) from prostatitis patients, thus confirming the initial findings that patients with prostatodynia have higher levels of self-reported pain and discomfort.

**Implication of psychophysiological observations**

These experiments suggest that patients with prostatodynia have increased levels of self-reported anxiety-related somatic discomfort and pain in comparison with healthy control subjects and patients with bacterial prostatitis. The symptom distress check-list scores provide some support for the proposition that prostatodynia is associated with a general behaviour pattern of excessive tension and the physiological measures demonstrate that these patients are generally more aroused than those with
prostatitis, the most marked differences being observed when measures of muscle tension and heart rate were observed under challenging conditions. It is, therefore, possible, as suggested by Segura et al. [2] that the symptoms of prostatodynia are indeed related to spasm of pelvic floor muscle, which is secondary to a general overactivity of skeletal musculature that occurs under stressful conditions. It is possible that resolution of the condition might be compromised by continuing muscle tension in the peri-prostatic region and pelvic floor of these patients.

**Urodynamic studies in prostatodynia and anxious bladder syndrome**

With techniques previously described elsewhere [6] patients with both prostatodynia and the anxious bladder syndrome have been investigated by means of medium-fill water cystometry. In view of the tendency to introspection and anxiety great care must be taken during the investigation of these patients and every attempt should be made to gain their confidence. All voiding studies are performed with the patient alone in the investigation room.

The initial mean maximum flow rate in 27 patients with prostatodynia was 16.2 ml/s [4]. Mean maximum urethral closure pressure was 121 cm water (Fig. 2) and all inflow studies demonstrated stable bladder function, the mean capacity at the normal desire to micturate being 320 ml. Voiding cystometry demonstrated a mean detrusor pressure of 34 cm water associated with a maximum flow rate of 11 ml/s.

Patients with the anxious bladder syndrome characteristically have a low and intermittent flow rate and the maximum urethral closure pressure is elevated to supranormal levels [6]. Inflow cystometry demonstrates a stable hypersensitive pattern and subsequent micturition studies show that the flow pattern is associated with a poorly maintained detrusor contraction wave (Fig. 3).

**Implication of urodynamic observations**

The urethral closure pressure in prostatodynia and anxious bladder syndrome is undoubtedly well above the normal range when comparison is made with age-matched controls [14] (Table 2). The raised pressure may be due to increased tone of adrenergic smooth muscle, intrinsic urethral striated muscle (external urethral sphincter), peri-urethral striated muscle or to a combination of these components. The perineal pain experienced by prostatodynia patients may presumably be either the cause or the result of this increased muscle tone.

It is interesting that both patient groups remain stable during inflow cystometry despite peri-urethral discomfort, which may be severe at the termination of filling. It seems reasonable to propose that these patients may possess a considerable capacity to inhibit (over-inhibit) detrusor contractions and such inhibitions may prevent the onset of the micturition phase. Studies during voiding show that the low flow rate of intermittent pattern in the patients with anxious bladder is due to low amplitude poorly maintained (but synergic) detrusor pressure waves. It is also possible that over-inhibition of the micturition reflex might result from the anticipation of discomfort arising from a hypersensitive urethra during voiding. Overt dysuria is, however, rather uncommon in these patients and it is equally possible that the observed effects are due to neurolog-
Sympathetic system and urinary tract dysfunction

Fig. 3. Micturition study in 'anxious bladder syndrome'. Poorly maintained detrusor contraction leads to poor and intermittent flow rate. Arrow: instructed to push in order to help commencement of flow. VV, Voided volume; RU, residual volume; F, flow; t, time; P, pressure [P\textsubscript{abd.}, abdominal; P\textsubscript{ves.}, vesical; P\textsubscript{det.}, detrusor (vesical minus abdominal)].

Table 2. Comparative data from patients with prostatodynia (four) and anxious bladder syndrome (six), compared with normal data from authors' personal series and studies reported by Abrams [14]

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Prostatodynia</th>
<th>Anxious bladder</th>
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<tr>
<td>Number</td>
<td>*</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>*</td>
<td>42</td>
<td>42</td>
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<tr>
<td>Mean maximal urethral closure pressure (cm water)</td>
<td>80–90</td>
<td>121</td>
<td>117</td>
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<tr>
<td>Mean inflow capacity (ml)</td>
<td>450–550</td>
<td>340</td>
<td>210</td>
</tr>
<tr>
<td>Mean subtracted detrusor voiding pressure (cm water)</td>
<td>60–70</td>
<td>34</td>
<td>42</td>
</tr>
<tr>
<td>Mean maximum flow rate (ml/s)</td>
<td>25–35</td>
<td>15</td>
<td>11</td>
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* Data derived from previous studies.

Discussion

The diagnosis of prostatodynia or anxious bladder will only be reached after a meticulous process of investigation has excluded all forms of recognized pathological disease of the lower urinary tract. However, when such investigations have been completed it is possible to identify groups of patients who show remarkable similarities to each other (the so-called 'sensory' disorders of micturition) [15] and it would seem probable that the clinical distinction between these dysfunctions is merely a reflection of the variable amount of psychological overlay that can be demonstrated in any particular groups of patients. Similar psychological studies have been made in female patients with the urethral syndrome [16].

The consistency of the urodynamic findings, when viewed together with the results of psychophysiological testing in these patients, seems to suggest that the observed urodynamic effects might be the result of a chronic anxiety state or overactivity of the sympathetic nervous system. Certainly the observed effects fit well with pharmacological studies in vitro which imply that chronic sympathetic activity would relax the dome of the bladder (?poorly maintained detrusor contraction) while maintaining excessive tonicity of the outflow tract (supranormal urethral pressure profile).Teleologically, a flaccid detrusor and a tightly contracted sphincter mechanism might be considered an ideal urological reaction to the sympathetically mediated fight and flight response.
It must, however, be emphasized that, despite the evident attraction of such theories, no definite cause–effect relationship has been established between objective measures of sympathetic nervous system activity and urodynamic findings in the lower urinary tract. It has to be recognized that similar observations might possibly be produced by an occult neuropathy or myopathy which cannot presently be detected by routine methods [17], and the hypothesis that underactive detrusor function is due to sympathetic overactivity will require further dynamic and synchronous measurements of adrenergic and urodynamic behaviour. Nevertheless it is reasonable to conclude that the observed responses do not deny the possibility that the sympathetic nervous system might exert an influence on the lower urinary tract in certain dysfunctional states and the pattern of this influence does not run contrary to that which might be expected from pharmacological experimentation.

References


DISCUSSION

**Andersson:** This was a very interesting paper. I should like to ask whether you have measured plasma catecholamines in these patients? Or if you plan to do it, because that might give some answer to the question whether or not there is a raised sympathetic activity.

**George:** We have attempted to do this, but I am sure you are aware that it is extremely difficult — at least I have found it very difficult — to establish good baseline conditions in order to measure plasma catecholamines, especially in these very over-aware young men. I am not happy that our baseline measurements are satisfactory. So the answer to the question is no, although clearly it would be nice to have such recordings.

**Andersson:** It would also be interesting to know whether or not these men are impotent.

**George:** All urologists will recognize this group — many of them actually present in the infertility clinic with impotence. Whether this is completely psychological or a local target organ problem, I just cannot say. But they do present with problems of erection.

**Stanton:** I hate to tread across the demarcation line. Why did you not refer them to a psychiatrist who might have told you why they were anxious?

**George:** I think this is what eventually happens, but, of course, this is a diagnosis of exclusion. Quite a few Americans do say that you should not spend all this money investigating the patients but send
them straight to a psychiatrist. But of course, every now and again you will miss something very important, and I think that it is essential that they go through the full screen before you can say that this is psychological in origin. I have not mentioned this, but, of course, we have treated this group with α-blockers, with significant success.

*Abrams:* You cannot really leave it at that. What do you mean by significant success?

*George:* Response to phenoxybenzamine was significant and resulted in a cure in about 50% of the patients, which I know does not sound very much, but in this group of patients it is a major triumph. And those patients have remained to this day so-called cured. They no longer attend the clinic.

*Abrams:* Do they still take phenoxybenzamine?

*George:* No, it was usually withdrawn between 3 and 6 months — slowly.

*Turner-Warwick:* Just as a clinician's view of this situation, for others in the room who are not clinicians, I recognize your control group. I think, I can identify the same patients. I have not the slightest idea what you call prostatitis any more. But of course, we have treated this group with phenoxybenzamine, because if there is one thing it is not related to, it is the prostate.

The problem is a dysfunction of bladder function, a dysfunction of the bladder neck and a dysfunction of the distal sphincter. The one part of the urethra which is open, as you say, is the mid-prostatic urethra. So I do not think this rather conceptual emotional term, prostatodynia, is really a good one.

When you are looking at this group of patients which we all see, who come in often referred by a psychiatrist, there are, I am sure you would agree, two very real groups. The man who is very worried cannot pass his water properly — you do a flow rate and you identify it as low — it is very important to recognize that there are also a number of these people who have high pressure bladders and they have a true dyssynergic mechanism. Some of these patients — the low pressure ones — also have a sort of relative dyssynergic bladder neck obstruction. Although we know it is very bad to treat a low pressure voiding inefficiency located at the bladder neck just like that, there are some that actually respond very well to it. So I think it is an amorphous group. I would not like the less clinical elements of the audience to go away with the impression that all people who complain of not being able to pass urine in public do in fact have low pressure. I think some of them have very real high pressure, as I am sure you agree.

*George:* Yes. Obviously, this is completely right.

A low flow rate must be investigated in a man of this age by pressure-flow studies. Clearly people with slow flows are anxious. There is no doubt about that. As to the previous point, I disagree. Before Drach introduced the term 'prostatodynia' — from his Greek upbringing — in 1978, you will be aware that there were a number of terms — pelvic floor tension, automobile rider's disease, and many other different phrases to cover this group of patients. He said it should all be consolidated and he invented this word, which at least does have the benefit that we all know what we are talking about. I completely agree it is nothing to do with the prostate.

*Turner-Warwick:* You know what you are talking about.

*George:* Better than pelvic floor tension myalgia.

*Corcoran:* Did you at any stage get normal flow rates on these patients? Did they have large residual volumes and did these volumes change after phenoxybenzamine? And did you try something like diazepam rather than phenoxybenzamine for any of your patients?

*George:* I am obviously extremely interested as to whether a low pressure/low flow system in a man of 32 would develop into a difficult chronic retention in later life. None of these patients, and this was characteristic, had a residual urine at all. They were all low volume stable bladders, and they micturated, albeit slowly, to completion. Certainly, we did use baclofen, diazepam, striated muscle blockers at whatever level we could think of, because pelvic floor tension implied that one should try these drugs. One 1981 paper was a three-arm trial: placebo v phenoxybenzamine v baclofen. But I routinely tried diazepam, as do many other people.

*Stanton:* My previous question was not facetious. I meant it very sincerely, because this small paper seems to illustrate what is a terribly important fact, that probably what is going on here is a primary brain problem rather than a bladder problem. Perhaps one of the first things — as you explained that the patient is basically urodynamically normal apart from the low flow/low pressure — is surely to treat the brain problem, to which the bladder problem is secondary. Hence the concept of the psychiatrist seeing them because of the anxiety state.

*George:* Yes, I fully support this. I think it is a tragedy when a women undergoes the standard treatment of urethral dilatation, several more urethral dilatations, YV-plasty and the operation for incontinence.

*Essenhigh:* At the risk of being boring, could I ask for a precise definition of prostatodynia, because I do not use the term. I do not like it; I recognize a whole heap of different groups of conditions which are valid for me, but may not be valid for you. I recognize what you are talking about
urodynamically, but what does this group come in complaining of? I suspect I know, but I should like to know what particular symptoms they are complaining of?

George: They are complaining of hesitancy, poor stream and frequency, largely by day and rarely, curiously, by night, patients in whom thorough and full urological investigation excludes all possible cause for this, and this includes examination of fractional urine and prostatic secretion cultures. No cells or bacteria are allowed in the prostatic secretion, that is absolutely essential.

Abrams: Did you say they have pain or not?

George: I forgot the primary symptom — pain. The other things I mentioned are important, but secondary. Perineal pain behind the scrotum.

Abrams: I agree with Richard Turner-Warwick and David Essenhigh, prostatodynia is an almost meaningless term, because what you describe as prostatodynia I recognize as an entity, but I also recognize a lot of younger men who have trouble voiding, who complain of hesitancy, slow stream and frequency, who never have pain, and they fit into your group beautifully. They are usually low pressure/low flow voiders.

George: Yes, I recognize a group I call the anxious bladder, who are exactly the group I presume you are talking about. There are shades of opinion, certainly. The overtly anxious patients I find complain more of micturition disturbances than of pain, and the opposite is the case of prostatodynia. How can one discuss it without having a word?

Abrams: I agree it is a problem.

Kirby: Could I ask how you measured the urethral pressure? I just wonder whether, if you did it by pulling a catheter down the urethra in these rather anxious men, whether it is a real observation that there is a chronically high resting urethral pressure, or whether this is just an artifact induced by anxiety and reflex spasm of the pelvic floor as the catheter is pulled out.

George: Yes, that is a very valid point. As they are pull fluid profiles, the only point I would make is that it is not totally anyway an artifactual profile because it is repeatable. I think most people agree that you cannot sustain a pelvic floor concentration for more than about 15 s, and you can do pull profiles getting a good symmetrical profile for longer than this if you wish. Secondly, they can increase this profile by voluntary squeeze, still on top of the 150 they are putting up on the routine profile. Thirdly, we have done urethropograms, and this, of course, means a catheter is in the anterior urethra well away from the sphincters, and in these cases, it is seldom possible, in our experience, to introduce contrast into the bladder: the external sphincter spasm can be seen to be very tight. I think it does genuinely reflect increased resting pelvic floor tone, cause unknown.