J Neurol (2002) 249 : 1–8

Oscar Fernández

Mechanisms and current treatments of urogenital dysfunction in multiple sclerosis

Received: 24 July 2001
Accepted: 25 July 2001

O. Fernández, MD
Neurological Service
Complejo Hospitalario Carlos Haya
Avda. Carlos Haya
29 010 Málaga, Spain
Tel.: +34-952/6 45-7 74
Fax: +34-952/6 45-7 96
E-Mail: ofernand@hch.sas.cica.es

Abstract The majority of patients with multiple sclerosis (MS) suffer from lower urinary tract symptoms and sexual dysfunction at some stage of the disease. This has a negative impact on the quality of life of patients as well as causing concern to caregivers and family. Neurologists can now treat most of these symptoms by a number of pharmacological and non-pharmacological methods. This review presents the neuroanatomy, neurophysiology, neuropharmacology and pathophysiology of the urinary bladder and sexual organs, and the biological mechanisms underlying urogenital dysfunction in MS patients. Current treatment options for urinary and sexual dysfunction are reviewed. As most urogenital symptoms of MS can now be treated by conservative means, expert urological or gynaecological consultation should be requested only if more aggressive diagnostic or therapeutic measures are needed.

Key words Multiple sclerosis · Urogenital dysfunction · Treatment

Introduction

Multiple sclerosis (MS) is the most frequent chronic neurological disease affecting young persons in developed countries. The cause of MS is not known, but it is supposed that genetic susceptibility and unknown environmental factors underlie the disease. MS is characterised by multiple lesions throughout the neuraxis, causing symptoms that can affect all neurological functional systems.

The majority of MS patients suffer from lower urinary tract symptoms and sexual dysfunction at some stage of the disease. Many efforts have been made to study and treat urogenital problems in MS. These complaints should be brought to the attention of treating neurologists, particularly since many of these problems are currently susceptible of improvement with symptomatic treatment. Adequate treatment can prevent further complications, resulting in an overall increase in the quality of life for MS patients.

Neuroanatomy, neurophysiology, neuropharmacology and pathophysiology of the urinary bladder and sexual organs

Urinary bladder

The urinary bladder and urethra serve to store and to expel urine. These complex functions are achieved through the co-ordination of the autonomic, somatic and central nervous systems (Table 1, Fig. 1).

The parasympathetic and the sympathetic divisions of the autonomic nervous system innervate the musculature of the bladder. The parasympathetic outflow originates in the sacral parasympathetic nucleus in the intermediolateral cell column of the spinal segments S2 to S4. Preganglionic neurons send their fibres through the ventral spinal nerves to form part of the pelvic nerves that synapse with postganglionic neurons in the pelvic plexus or in the intramural ganglia within the bladder. These neurons use acetylcholine as a neurotransmitter,

Table 1 Innervation of the bladder

Division	Spinal cord	Nerve	Neurotransmitter	Receptor	Mechanism	Effect
Parasympathetic	S2 to S4	Pelvic	Acetylcholine	Muscarinic	Contraction of detrusor Relaxation of outlet (urethra)	Bladder emptying Bladder emptying
Sympathetic	T10 to L2	Hypogastric	Norepinephrine	Beta Alpha	Relaxation of detrusor Contraction of outlet (urethra)	Retention of urine Retention of urine
Somatic	Efferent: S2 to S4 Afferent: S2 to S4	Pudendal	Acetylcholine	Nicotinic	Contraction of external sphincter	Retention of urine

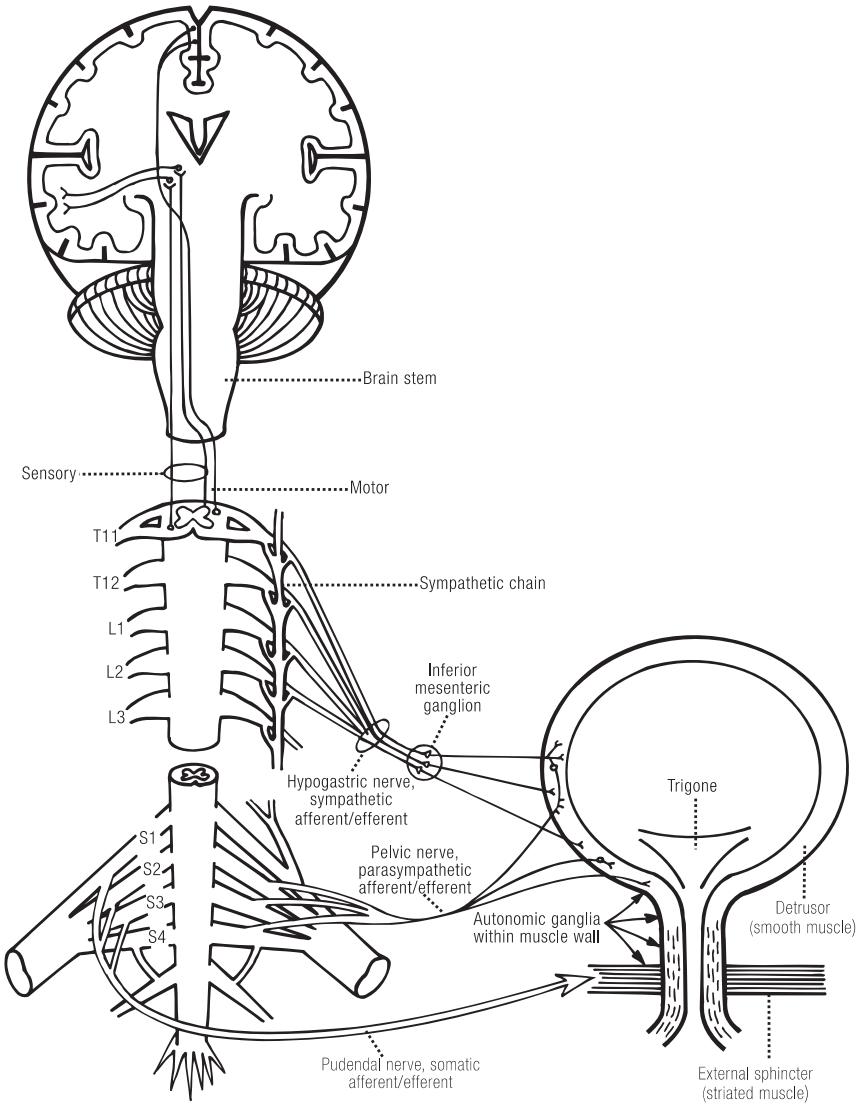

Fig. 1 Schematic diagramme of normal bladder neuroanatomy

and mediate their action via cholinergic receptors in the bladder by activating the bladder detrusor muscle and relaxing the bladder neck (internal sphincter), which promotes bladder emptying, or micturition.

The lumbar sympathetic innervation arises at the spinal segments T10 to L2 and their fibres are carried into the hypogastric nerves, use norepinephrine as neurotransmitter and produce relaxation (beta receptor) of the detrusor muscle and contraction (alpha receptors) of the bladder neck, favouring storage or continence of urine.

The somatic innervation is provided by neurons located in the spinal segments S2 to S4 that send their fibres through the pudendal nerve, that activate contrac-

tion of the external sphincter (voluntary) via nicotinic cholinergic receptors, producing urine retention.

Micturition centres are located in the region of the pons, a medial region that gives rise to excitatory input to the sacral parasympathetic neurons that innervate the detrusor muscle and a lateral region that sends excitatory input to sacral somatic motor neurons that innervate the external sphincter. During micturition, the medial region is activated and inhibits the lateral region. This activity produces co-ordinated detrusor contraction and external sphincter relaxation, resulting in bladder emptying. The interruption of descending pathways in spinal cord lesions produces uncoordinated activity of these groups of neurons, producing detrusor-sphincter dyssynergia.

The higher control of micturition is located in the medial frontal cortex and the diencephalon. Cortical input is responsible for voluntary control of the initiation and the cessation of micturition.

There are mechanoreceptors (volume and tension receptors) that send their input through the pelvic nerve to the sacral roots S2 to S4. Pain fibres from the bladder base submucosa travel via the hypogastric nerve to the spinal column between T10 and L3 and ascend in the lateral spinothalamic tracts. Muscle propioceptors in the external sphincter and pelvic floor send their fibres through the pudendal nerve to the sacral segments S2 to S4. The sensory fibres feed back to the sacral parasympathetics to form the micturition reflex arc.

During urine storage, bladder distension triggers low level filling of bladder afferents. This stimulates sympathetic outflow, causing inhibition of the detrusor and contraction of the internal and external sphincters of the bladder. In normal conditions, micturition is a reflex triggered by stimulation of tension receptors and integrated at spinopontospinal circuits that co-ordinate the contraction of the detrusor muscle of the bladder and relaxation of the internal and external sphincters of the bladder. When the suprasegmental pathways are interrupted, micturition takes place via segmental spinospinal sacral reflexes triggered by perineal or nociceptive stimulation. Bladder and sphincteric contractions are uncoordinated producing detrusor-sphincter dyssynergia. If the lesion affects the higher control, i. e. frontal lobes, the result is involuntary micturition (inhibited bladder).

The parasympathetic preganglionic neurons and postganglionic fibres release acetylcholine (ACh), the latter activating muscarinic receptors M2 and M3 on the smooth muscle of the bladder and urethra. The M1 receptors on axons of the postganglionic neurons provide a negative feedback, inhibiting the release of ACh when activated by ACh. Nonadrenergic, noncholinergic (NANC) transmitters, (adenosine triphosphate, vasoactive intestinal peptide – VIP- and neuropeptide Y) act with ACh to contract the detrusor smooth muscle via the purinergic receptors, co-localised with the cholinergic receptors. The NANC transmitters modulate ganglionic transmission, leucine enkephalin (ENK) produced by preganglionic neurons and endothelin produced by non-neural tissues, and inhibits cholinergic transmission. VIP and substance P (SP) facilitate ganglionic transmission. Contraction of the urethral smooth muscle depends on cholinergic agonists. Relaxation of the urethra depends on non-cholinergic parasympathetic transmitters, particularly nitric oxide (NO).

Sympathetic postganglionic neurons release norepinephrine, which acts on β–2 adrenoceptors, relaxing the bladder detrusor and, via the α–1 adrenoceptor, producing contraction of the smooth muscle of the urethra and bladder base. Noradrenergic innervation is more complex in the male proximal urethra, preventing retrograde ejaculation.

The striated muscles of the external sphincter receive cholinergic innervation via the pudendal nerve. ACh activates nicotinic receptors evoking a contraction. These striated fibres receive also noradrenergic input, uniquely receiving both autonomic and somatic afferents.

Sensory afferents contain pituitary adenylate, glutamate, VIP, SP, calcitonin gene-related peptide, ENK, cholecystokinin and NO, implying that these substances play a role in micturition.

The pontine micturition centre is under tonic inhibition by ENK containing neurons (naloxone, an opioid antagonist, decreases the volume at which the micturition reflex occurs). Glutamate and dopamine receptor activation facilitates voiding via pontine and spinal mechanisms. Glycine, GABA and 5-HT are neurotransmitters acting probably as voiding inhibitors.

Due to this complex neuropharmacology, drugs may act on multiple sites with opposing effects on bladder function.

Sexual organs

Sexual activity in humans relies upon a complex series of neurally mediated phenomena, occurring in a hormonal milieu. It is necessary that each component involved in sexual activity functions adequately, including psychological factors, endocrine system, erectile corporal bodies, nervous pathways and blood supply.

Erectile tissue lies within two dorsal corpora cavernosa and a ventral corpus spongiosum, the latter containing the urethra. A layer of fibrous tissue named tunica albuginea surrounds each corpus, and a common layer named Buck's fascia surrounds all three. The corpus cavernosum is composed of cavernous spaces surrounded by smooth muscle cells. The corpus spongiosum has larger cavernous spaces, smaller trabeculae and fewer smooth muscle cells.

The blood supply of the penis is derived from the pudendal arteries, which are branches of the hypogastric arteries. The pudendal artery supplies the posterior scrotum and the urethra and then divides into the dorsal and central arteries of the penis. The paired dorsal arteries course between the Buck's fascia and the tunica albuginea. The primary blood supply to the erectile tissue of the corpora cavernosa is the paired central arteries and numerous branches of these arteries; the helicine arteries empty directly into the cavernous spaces. The venous drainage occurs through venules located below the tunica albuginea that form emissary veins traversing the tunica albuginea and drain into one of four drainage systems: The superficial dorsal vein, the deep dorsal vein, the cavernous veins and the urethral veins.

The parasympathetic innervation is derived from cell bodies located in the sacral S2 to S4 spinal cord, course through the pelvic nerve, synapse in the pelvic ganglia and afterwards form the paired cavernosal nerve. The sympathetic innervation arises in neurones located at the spinal segments T10 through L2, courses through the paired hypogastric nerves to the pelvic ganglia plexus, entering afterwards into the cavernosal nerves together with the parasympathetic fibres.

The perineal striated musculature is innervated by somatic efferents from the S2 to S4 level via the pudendal nerve. The sensory innervation of the penis is carried to the S2 to S4 segments in the dorsal nerve of the penis, a branch of the pudendal nerve (Table 2).

The higher neural control is the cortex that receives sensory input from the penis. Thalamic and cortical areas generate sexual feelings and genital sensation, but do not generate erectile response, which probably is mediated primarily in the hippocampus.

The primary events leading to erection are increased parasympathetic outflow, dilation of vascular inflow, smooth muscle relaxation of the corpora cavernosa, engorgement of vascular sinusoids, compression of emissary veins, decreased corporal venous outflow with maintained arterial inflow and trapping of blood within the corpora because of increased venous resistance.

Increased sexual sensory and psychogenic excitation results in accentuated sympathetic outflow acting via adrenergic neurons on the bladder neck, vas deferens, seminal vesicles, epididymis and prostate. This triggers ejaculation, producing contraction of sinusoidal smooth muscle, forcing corporal blood out of the corporal bodies, making emissary veins become less angulated and freeing venous blood flow from corpora, with a subsequent reduction in the intracorporal pressure and detumescence.

The parasympathetic nerves have ACh as neurotransmitter. However, the NANC pathways, co-localised with the parasympathetic which decrease smooth muscle tone via NO and VIP, are more relevant. In physiologic conditions NO is released from cholinergic and NANC neurons and mediates the relaxation of vascular smooth muscle in the corporal sinuses, resulting from increased adenosine monophosphate (AMP) and guanosine monophosphate (GMP). The sympathetic adrenergic fibres activate α–1 adrenoceptors, increasing corpora smooth muscle tone and producing detumescence. A separate parasympathetic cholinergic pathway indirectly modulates tone by altering sympathetic outflow. There are endothelial cells in the corpora that produce endothelin, which is a potent vasoconstrictor. Prostaglandins (PG) are also involved in muscle relaxation (PGE1, PGE2), or contraction (PGF2 and thromboxane A2).

From a pathophysiological point of view, erectile dysfunction can be classified as psychogenic, neurogenic, arterial, cavernous, venous and endocrinologic. Frequently more than one disorder is present.

Female innervation, although less studied, is considered in general terms to be similar to that of the male.

Table 2 Innervation of the penis and clitoris

Division	Spinal cord	Nerve	Neurotransmitter	Receptor	Mechanism	Effect
Parasympathetic	S2 to S4	Pelvic-Cavernosal	Acetylcholine NANC	Muscarinic co-localised receptors	Vascular dilation Smooth muscle relaxation	Reflex erection
Sympathetic	T10 to L2	Hypogastric – Cavernosal	Norepinephrine	Adrenoceptors	Contraction of bladder neck, vas deferens etc. Contraction of smooth muscle	Ejaculation Detumescence
Somatic	Efferent: S2 to S4	Pudendal	Acetylcholine	Nicotinic	Contraction of perineal striated musculature	Orgasmic contractions
	Afferent: S2 to S4	Pudendal	Acetylcholine	Tactile and pain receptors (slow and rapid adapting)	–	Reflex erection

Urinary dysfunction in multiple sclerosis

Clinical manifestations and diagnosis

It has been reported that there is a correlation between the duration of MS and disability [11]. In the early stage of the disease, a low percentage of MS patients have urological complaints, sometimes associated with other neurological symptoms [13, 18], although there may be evidence of urological dysfunction in clinically silent patients [3]. During the course of the disease, most patients with MS develop urinary symptoms, women and men being equally affected. In one series, symptomatic voiding dysfunction was present in 97 % of the patients, urgency and frequency in 32 %, incontinence in 49 %, and hesitancy-retention in 19 % [8]. The best-known series [9] addressing urinary symptoms in multiple sclerosis is summarised in Table 3. The differences between figures are at least in part due to methodological factors, e. g. cohorts were from different hospital settings and different stages of MS.

Five possible urodynamic patterns can be found in MS [11]:

a) Detrusor hyperreflexia without obstruction hyperreflexia
b) Detrusor hyperreflexia with outlet obstruction (detrusor external sphincter dyssynergia – DSD)
c) Detrusor hyperreflexia with impaired contractility
d) Detrusor areflexia
e) Normal function.

The most common urodynamic finding is detrusor hyperreflexia; the bladder contracts involuntarily and the person experiences a feeling of imminent micturition. Incontinence can be avoided sometimes by contracting the pelvic muscles, but the pressure can be so great that, despite the contraction of the external sphincter, urine escapes from the bladder, resulting in urge incontinence. Urodynamics might not be necessary in a patient with urinary urgency and mild to moderate paraparesis, because symptoms in the bladder of an MS patient can be reasonably assumed to be due to detrusor hyperreflexia that responds to anticholinergics [4].

Bladder hyperreflexia and DSD often coexist. In this case, both the external sphincter and the detrusor contract involuntarily at the same time. There is hesitancy, interrupted urinary stream and incomplete bladder emptying. DSD is very frequent in MS, affecting approximately two-thirds of patients [6]. Detrusor areflexia is uncommon in MS [4].

The goals in MS are to increase the interval between micturitions, to complete bladder emptying, reduce incontinence, prevent urinary tract infections as well as urological complications related to detrusor external sphincter dyssynergia, high detrusor filling pressures (> 40 cm H2O) and presence of an indwelling catheter. All these factors predispose to upper tract problems (10 % of patients), including vesicourethral reflux, bladder and kidney stones, hydronephrosis, pyelonephritis and renal insufficiency.

In every MS patient, a detailed clinical history should be obtained, with emphasis on symptoms of urgency, frequency, incontinence, hesitancy, retention and nocturia [1, 2, 5]. A voiding diary, including frequency and 24-hour urine volume, should be recorded. Post-void residual (PVR) should be recorded, preferably by ultrasonography, but if this is not available it can be done by catheterisation after spontaneous voiding, measuring the residual urine.

Laboratory tests should include: urine analysis, culture and sensitivity, postvoid residual, urodynamics, voiding cystogram and occasionally a cystoscopy. The non-invasive tests might be performed annually or more frequently, if needed. Invasive tests should be performed under formal expert urological supervision, but are only occasionally needed. Indications for urodynamic evaluation are: monitoring of voiding pressures, evaluation of symptoms (frequency, urgency, incontinence), large postvoiding residual volumes of urine (retention), recurrent urinary tract infections, deterioration of upper tracts and evaluation and monitoring of pharmacotherapy.

Table 3 Percentages of patients affected by symptoms of bladder dysfunction in multiple sclerosis cohorts (modified from Hennessey et al. 1999).

Study	Urgency	Frequency	Urge incontinence	Hesitancy	Retention
Sachs 1921	31	–	37	49	–
Langworthy 1938	54	33	34	40	–
Carter 1950	24	17	50	–	17
Miller 1965	60	50	36	33	2
Bradley 1973	86	60	–	28	20
Philp 1981	61	59	47	25	8
Goldstein 1983	32	32	49	–	–
Awad 1984	85	65	72	36	–
Gonor 1985	70	48	56	30	–
Betts 1992	85	82	63	49	–
Hennessey 1999	71	76	19	48	–

Treatment

Treatment must be individualised for every patient [7]. Treatment has to be adapted to the phase of the disease, the symptoms, and the results of non-invasive tests. Possible causes of clinical exacerbation such as urinary tract infections should be prevented and treated as soon as possible.

When urodynamic studies are not considered necessary, or not immediately available, patients should be treated conservatively, using timed voiding, limiting fluid intake, suprapubic tapping to trigger micturition, clean intermittent catheterisation and use of diapers. In a disease as variable over time as is MS, irreversible or ablative surgery should be avoided unless it has been confirmed that the voiding pattern and urodynamic findings have stabilised over time. In case of doubt, specific treatment strategies should be based on urodynamic findings, because starting or changing medication without urodynamics can sometimes induce more harm than benefit. A permanent indwelling catheter should be avoided whenever possible.

Detrusor hyperreflexia with small PVR (< 100 ml) usually responds to anticholinergic agents, for example oxybutinin (Ditropan) 5 mg BID or TID, propantheline bromide (Pro-Banthine) 15 mg TID, or tolterodine (Detrol) 2 mg BID, which causes less side effects. Overdose can result in urinary retention. Sometimes it is useful to add tricyclic medication.

Detrusor hyperreflexia with DSD can be treated with antispasticity medication (baclofen or tizanidine) and/or α1-blockers (terazosin, doxazosin, tamsulosin). When PVR (> 100–150 ml) is significant, patients respond better with a combination of anticholinergic agents plus intermittent self-catheterisation (ISC). In this situation, the Credé and suprapubic tapping manoeuvres are contraindicated, because of the risk of inducing urethral reflux.

Detrusor areflexia with low PVR (150–200 ml) can be treated with trigger manoeuvres and timed voiding, or ISC every 12 hours. Patients with PVR > 250 ml should be treated with ISC 4–5 times per day.

Patients with bladder dysfunction should acidify urine with supplements of cranberry juice, or 1–2 grams of vitamin C per day. Severe nocturia that is not responsive to evening fluid restriction, anticholinergics and ISC can be treated with desmopressin acetate nasal spray (10–20 μg) given at bedtime. In this case it is necessary to monitor the serum sodium for 1–3 months to avoid drops in serum sodium.

In cases of urge incontinence or post-micturition dribbling, devices for men are available (penile sheath or urinal condom), as well as absorbent products for patients of both sexes.

Intravesical capsaicin in doses of 1 mmol/liter in 30 % alcohol increases the bladder capacity and reduces the amplitude of hyperreflexic contractions. This can be used in experienced centres for the treatment of intractable detrusor hyperreflexia.

Sacral nerve root stimulation with an implantable system can be used if urge incontinence and voiding dysfunction do not respond to pharmacological treatment.

Conservative management should be used as long as possible (Table 4). Surgical interventions in case of failure or less aggressive measures are indicated as follows:

a) Detrusor hyperreflexia without obstruction hyperreflexia:
   Augmentation cystoplasty, denervation procedures (Ingelman-Sundberg procedure, subtrigonal phenol or selective sacral rizotomy)

Table 4 Pharmacological treatment of urinary dysfunction

Facilitation of Storage		Facilitation of Voiding	
Drug	Action	Drug	Action
Anticholinergics	Detrusor contraction inhibition	Cholinomimetics	Contraction of detrusor
Propantheline bromide (Pro Banthine)		Bethanechol chloride	
Tolterodine (Detrol)		Carbamylcholine chloride	
Dicyclomine		Neostigmine	
Atropine		Acetyl-b-methacholine	
Sympathomimetics	Contraction of neck sphincter	α-Sympathetic block	Relaxation of neck sphincter
Ephedrine		Terazosin	
Pseudophedrine		Tamsulosin	
Phenilpropanolamine		Doxazosin	
Imipramine		Phenoxybenzamine	
Phenylephrine		Guanethidine	
		Methyldopa	
Muscle relaxants	Reduction of detrusor contraction capacity	Sensory input reducer	Incr. Bladder
Oxybutinin (Ditropan)		Capsaicin	
Dicyclomine (Bentyl)			
Flavoxate (Uripass)			
Imipramine (Tofranil)			

b) Detrusor hyperreflexia with DSD:
External sphincterotomy, indwelling urethral stent or urinary diversion
c) Detrusor areflexia:
Urinary diversion.

Sexual dysfunction in multiple sclerosis

Clinical manifestations and diagnosis

Male erectile dysfunction alone is extremely unlikely as the presenting symptom of MS, although it has been reported to occur associated with other symptoms in 1 % of males [15].

After several years, the appearance of sexual dysfunction is common in MS, affecting approximately 70 % of patients [14]. To a considerable extent, sexual dysfunction in MS is due to neurogenic lesions, but a psychological component and the side effects of medication always have to be considered. Men report decreased libido, difficulty in achieving or maintaining erection, delayed ejaculation, loss of ejaculatory function and an impaired genital sensation. Women experience decreased libido (60 %), orgasmic dysfunction (40 %) and decreased vaginal lubrication (36 %), as well as a decreased vaginal sensation [10].

Factors correlated with sexual dysfunction are disease duration, spasticity, and bladder and bowel problems, as well as fatigue and depression [12].

For the most part, neurogenic erectile dysfunction requires minimal investigations, because no reliable tests are available at present. A serum testosterone determination permits the discarding of hormonal aetiology and the penile tumescence test for monitoring nocturnal erection may help to differentiate an organic from a psychogenic aetiology. Other neurophysiological or vascular studies are not recommended, or needed in general in MS. They are used sometimes in specialised centres to study other causes of erectile dysfunction that can be coincident with MS. Gynaecological examination for women and urological examination for men are recommended, in some countries, as part of the initial investigations.

Treatment.

Previous considerations

- Psychological aspects
  Patients with MS tend to have negative expectations, inhibiting sexual desire and performance. A multidisciplinary approach, including the participation of the sexual partner, is important.

Table 5 Medications that impair erectile function

Antidepressants	Amitriptyline, imipramine, fluoxetine, etc.
Anxiolytics	Benzodiazepines
Antihypertensives	Diuretics
	Sympatholytics: – acting centrally (methydopa, clonidine) – acting peripherally (e. g. reserpine, guanethidine) – beta-blockers (e. g. propranolol, atenolol, metoprolol) – alpha-blockers (prazosin, terazosin, doxazocin)
Cardiovascular drugs	Digoxin
	Antiarrhythmics (disopyramine)
Antineoplastics	Alkylating agents
Hormonal therapy	Antiandrogens
	Estrogens
	Glucocorticoids
	Progestagens
Antipsychotics – Neuroleptics	Phenothiazines
Antihistamines	H2 blockers
Anticonvulsants	Phenitoin
Anticholinergics	Trihexiphenidil, etc.
Other	Alcohol, Tobacco

- Somatic aspects
  Concurrent medical conditions must be adequately treated before approaching the treatment of the sexual dysfunction (e. g. diabetes, hypertension, endocrine or nutritional alterations).
- Pharmacological aspects:
  Medical treatments very often affect erectile function negatively (see Table 5).

Specific therapy

- Stimulation therapy
  To facilitate psychogenic erections, the use of erogenous zone development, erotic visual or audio aids as well as olfactory stimulation can be used. Manoeuvres to enhance the development of reflex erectile activity are manual and vibratory stimulation. Should these therapies fail, the techniques outlined below may prove effective.

- Medical therapy

  - **Oral medication** *Yohimbine* blocks α2-adrenergic receptors and can be used at a dose of 5.4 mg TID, although there is little evidence of efficacy.
    L-Arginine is an amino acid precursor to the formation of NO, that mediates the relaxation of vascular smooth muscle in the corporal sinuses resulting from increased cAMP and cGMP.
    Apomorphine is used in Parkinson's disease due to its dopaminergic activity, and an augmented erectile response has also been described. Side effects have limited its use.

Sildenafil (Viagra™): NO released from cholinergic and NANC neurons, induces the enzyme guanylate cyclase and produces increased levels of cGMP within the corporal smooth muscle, being cGMP itself that causes the smooth muscle relaxation, initiating the erectile response. Doses of 50–100 mg should be administered 1 hour prior to intercourse. This can enhance the effect of nitrates producing hypotension; this combination should be avoided.
Trazodone, a serotoninergic receptor agonist, has been associated with the development of priapism in men and women in doses of 100–200 mg at bedtime.

- **Topical therapy** Prostaglandin E1 (Alprostadil) in doses of 125–1000 μg has been used with partial success by intraurethral application.

- **Intracavernosal therapy** Prostaglandin E1 by the intracavernosal route is an efficacious form of treating erectile dysfunction. Complications are priapism, pain and scarring of the tunica albuginea with a permanent curvature of the erect phallus. Transient side effects are headache, flushing, dyspepsia, rhinitis and alterations in perception of colour or brightness. Other effective intracavernosal therapeutic agents are papaverine, phentolamine and moxisylite. Combinations of these drugs can also be used.

- External devices
  A vacuum device produces penile rigidity that has to be maintained with constriction bands to avoid venous return.

- Surgical therapy
  Inflatable, rigid or semirigid penile prostheses may be used in refractory cases.

Conclusion

Urogenital symptoms are rare at the onset of MS, but become very frequent during the course of the disease, leading to a negative impact on the quality of life of patients, and concern to caregivers and family. Neurologists can now treat the majority of these symptoms with conservative means. Expert urological or gynaecological consultation should be used only if more aggressive diagnostic or therapeutic measures are needed.

References

1. Andrews KL, Husman DA (1997) Bladder dysfunction and management in multiple sclerosis. Mayo Clinic Proc. 72:1176–1183.
2. Appel RA (1995) Evaluation and management of urologic disorders in multiple sclerosis. Multiple Sclerosis 3:6–9
3. Bemelmann BL, Hommes OR, Van Kerrebroek PE, et al. (1991) Evidence for early lower urinary tract dysfunction in clinically silent multiple sclerosis. J Urol 145:1119–1124
4. Betts CD, D'Mellow MT, Fowler CJ, et al. (1993) Urinary symptoms and the neurological features of bladder dysfunction in multiple sclerosis. J Neurol Neurosurg Psychiatry 56:245–250
5. Betts CD (1999) Bladder and sexual dysfunction in multiple sclerosis. In: Fowler CJ (ed.): Neurology of bladder, bowel and sexual dysfunction. Butterworth-Heinemann. Boston, pp: 289–308
6. Blaivas JG, Barbalias GA (1984) Detrusor-external sphincter dyssynergia in men with multiple sclerosis: an ominous urologic condition. J Urol 131:91–94
7. Fowler CJ, Kerrebroeck PE, Nordenbo A, et al. (1992) Treatment of lower urinary tract dysfunction in patients with multiple sclerosis. Committee of the European Study Group of SUDIMS. J Neurol Neurosurg Psychiatry 55:986–989
8. Goldstein I, Siroky MB, Sax S, et al. (1982) Neurologic abnormalities in multiple sclerosis. J Urol 128:5412–5545
9. Hennessey A, Robertson NP, Swingker R, et al. (1999) Urinary, faecal and sexual dysfunction in patients with multiple sclerosis. J Neurol 246:1027–1032
10. Hulter B, Lundberg PO (1995) Sexual function in women with advanced multiple sclerosis. J Neurol Neurosurg Psychiatry 59:83–86
11. Koldewijn EL, Hommes OR, Lemmens WAJG, et al. (1995) Relationship between lower urinary tract abnormalities and disease related parameters in multiple sclerosis. J Urol 154:169–173
12. Mattson DH (1995) Sexual dysfunction in multiple sclerosis. Multiple Sclerosis 2:10–13
13. Miller H, Simpson CA, Yeates WF (1965) Bladder dysfunction in multiple sclerosis. BMJ 1:1265–1269
14. Minderhoud JM, Leehuis JG, Kremer J, et al. (1984) Sexual disturbances arising from multiple sclerosis. Acta Neurol Scand 76:299–336
15. Müller R (1949) Studies on disseminated multiple sclerosis. Acta Neurol Scand 222:67–71