Urogenital dysfunction in patients with multiple sclerosis

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Abstract: The occurrence of urogenital dysfunction as an isolated early symptom in multiple sclerosis (MS) is rare, but the prevalence thereof becomes high with progression of disease. Lower urinary tract dysfunction may add to the cause of death (particularly through urinary infections), but both urinary and sexual dysfunction significantly affect quality of life of patients.
Both storage and evacuation of urine may be affected by MS, and ultimatively the functional diagnosis can only be made by urodynamic testing. As upper urinary tract affection is, however, rare (and can be prevented by timely ultrasound imaging), a first stage diagnostics in the MS center by the neurologist and specialized nurse is appropriate. History, urine tests and post void residual urine determination (preferably by ultrasound) should provide necessary data for treatment of infections, and also symptomatic management of frequency, urgency and incontinence by bladder training, anticholinergics, and intermittent self catheterization (as indicated); the referral to urologist may be reserved for patients who fail first line treatment. Treatment in the late stages of MS is as yet little researched, but eventually a suprapubic catheter is the preferred method of bladder emptying.
Sexual dysfunction should be actively sought in MS patients (in men erectile and ejaculation dysfunction, in women deficient lubrication and genital hyper- or hyposensitivity are frequent). Clinical examination contributes little to clarification of neurogenic sexual dysfunction, but defines the extent of other deficits due to MS, which may be relevant for sexual counseling (spasticity, sensory loss). Sildenafil has been demonstrated to be effective in treatment of men, but not in women. Other management options exist, and the doctor and nurse in the MS center should be proactive in providing first line counseling and management.

Lower urinary tract dysfunction:

Introduction: The prevalence of urinary symptoms in any mixed patient group with multiple sclerosis is high; in a conservative estimate it is at least as high as that of lower limb dysfunction, and the MRI incidence of spinal cord lesions (c. 75%) (1). The estimates vary in different studies and it seems evident that the prevalence depends on the state of progression of disease; lower urinary tract dysfunction is a rare sole initial symptom (2% have been reported by Goldstein et al 1982, but also lower and higher numbers have been quoted) (2). In advanced multiple sclerosis, neurogenic bladder disease probably affects all patients.
Even in patients who are urologically asymptomatic and have a relatively short disease duration (mean 5 years) urodynamic abnormalities have been demonstrated in 52% (3).
Urogenital symptoms are recognised to have significant adverse effect on the quality of life in MS patients (4). Lower urinary tract dysfunction is furthermore a potentially serious (although not yet fully defined) health risk to patients. In a study of causes of death in USA, symptomatic urinary tract infection was considered as a contributing cause in 8.4% of cases; terminal renal insufficiency was, however, not found to be a notable cause of mortality (5).

Neural Control of Micturition Voluntary micturition is a behaviour pattern which starts with relaxation of striated urethral sphincter. The micturition center in the pons co-ordinates micturition as such, but areas rostral to the brainstem (the hypothalamus and other parts of the brain including the frontal cortex) are responsible for the timing of the start of micturition.
The pontine micturition center (PMC) co-ordinates the activity of motor neurons of the urinary bladder and the urethral sphincter (both nuclei located in the sacral spinal cord), receiving afferent input via the periaqueductal grey. This brainstem control of lower urinary tract function is organized as a on-off switching circuit that maintains a reciprocal relationship between the urinary bladder and urethral outlet. Without PMC and its spinal connections co-ordinated bladder/sphincter activity is not possible. Thus patients with such lesions demonstrate bladder sphincter discoordination (dyssynergia). Patients with lesions above the pons do not show detrusor-sphincter dyssynergia, they, however, suffer from urge incontinence (due to bladder overactivity), may demonstrate non-inhibited sphincter relaxation and furthermore an inability to delay voiding to an appropriate place and time.

Urodynamic abnormalities in MS: Urodynamic abnormalities were found in all MS patients complaining of lower urinary tract symptoms by Bemelmans et al. (3), but in other populations up to 30% of symptomatic patients have no demonstrable abnormalities (6). Typically, the most common urodynamic abnormality is neurogenic detrusor overactivity without bladder outlet obstruction (62%), than neurogenic detrusor overactivity with detrusor sphincter dyssynergia (25%), than detrusor underactivity (20%) (7).
Lower urinary tract symptoms and urodynamic abnormalities may worsen during the course of the disease and regular reviews of lower urinary tract status have been recommended (8).

Correlation of lower urinary tract abnormalities, clinical picture and MRI: Female patients have been said to be more commonly affected than males, but this as well as other correlations (age at onset, type of MS, etc.) are controversial. In both sexes urgency, frequency, nocturia and pain are common. More common in men are: hesitation, weak urine flow and incomplete bladder emptying. Incontinence is more frequent in women.
In principle, the lesions responsible for LUT dysfunction may be anywhere along the neuraxis, as the neural LUT control matrix is widely spread throughout the brain and spinal cord. MS plaques may conceivably even cause a ”lower motor neuron type” LUT dysfunction if affecting lower sacral cord segments (9). A correlation between lower urinary tract complaints and spinal cord cross sectional area as defined my MRI has been demonstrated. There is no good evidence for association of urinary symptoms and MRI changes in the brain (10).
With progression of disease (particularly it seems with increasing spinal cord involvement) there is worsening of lower urinary tract dysfunction. There may be worsening of detrusor overactivity, but particularly of the efficiency of detrusor contractions (bladder emptying). The worsening urinary problems are complicated / exacerbated by progressive loss of ambulation, spasticity and cognitive impairment.
Lower urinary tract dysfunction is accompanied by recurrent urinary tract infections, but rarely by upper urinary tract involvement and only exceptionally by renal failure. Indeed, renal failure seems to be no more common than in the general population (11).

Diagnostics: In addition to overall assessment of the clinical picture and the neurological deficit, a careful history of lower urinary tract symptoms is mandatory. The use of a validated questionnaire is promoted (12) It is useful if the patient fills in a voiding diary. Examination of the anogenital region including assessment of the anal sphincter tone, sensation of touch and pinprick, the bulbocavernosus and anal reflex (bilaterally) is traditionally a part of the overall neurological examination, but is often neglected. In the experience of the author, such examination is not only occasionally helpful (because of detection of some unexpected abnormality), but also convincing the patient that the neurologist is taking his/her complaints seriously.
As for investigations, no general consensus guidelines exist; in practice, in a MS patient developing LUT symptoms usually no additional diagnostics are performed to determine the neurological lesion responsible (i.e., imaging or neurophysiological testing). The practice related to an urological (urogynecological) consultation varies in different centers. Several tests are available to the clinician

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to asses the function of LUT; the more simple testing is practiced within many MS centers, but few neurological departments have an uroneurological unit providing the availability of a full urodynamic investigation.

Residual urine cannot be reliably ascertained from history. It can be measured after a normal void by an ''in-out'' catheterisation, or by a hand held ultrasound scanner. (It is important to note that the residual urine may not reflect detrusor contractility, because urine may be emptied by straining or pressure on the abdominal wall). Measurement of post void residual urine is particularly important before prescribing an anticholinergic drug for frequency, urgency and urge incontinence, as residual urine may in itself trigger uninhibited detrusor contractions (and certainly exacerbate the clinical situation in patients with neurogenic detrusor overactivity). Residual urine may occur only after introduction of an anticholinergic drug (as a common side effect), and may be the reason why the drug seems to be non-effective. It is accepted that the determination of the post void residual urine is required in neurological patients with LUT symptoms.

Uroflowmetry non-invasively measures urinary flow and provides information on urine flow vs. time (the uroflow ''curve''). Maximum and mean flow rates as well as the voided volume can be established. A ''poor'' flow may be due to detrusor failure or bladder outlet obstruction. The measurement is only valid if the voided volume exceeds 150 ml, which may be a problem in neurological patients. Combined with ultrasound measurement of post void residual urine uroflow is a screening test to exclude serious bladder outflow obstruction. (Outflow obstruction may be deleterious to the upper urinary tract and needs further diagnostics).

Cystometry records bladder pressure in relation to its volume. It is an invasive test which provides data on detrusor function and also sensation in the bladder. In the filling phase of the ''micturition cycle'' (filling cystometry) the test assesses the storage capability of the bladder. In the voiding phase (voiding cystometry) the relationship between detrusor pressure and uroflow its recorded, and the ''mechanics'' of micturition is assessed. With concomitant imaging and/or electromyographic recording of external sphincter activity detrusor – (external) sphincter dyssynergia can be demonstrated. Ureteric reflux and the site of neurogenic bladder outlet obstruction can be best visualised by videourodynamics. The role of cystometry (and videocystometry) in the investigation of neurological patients with bladder dysfunction has been promoted by urologists, because it is only through these investigations that detrusor sphincter dyssynergia can be diagnosed (13). The International Consultation on Incontinence Consensus recommends that patients with suspected neurogenic LUT dysfunction should receive comprehensive urodynamic evaluation (including videourodynamics, if possible) to establish the state and function of LUT (14). Because upper urinary tract involvement is rare in MS patients it has been argued that urodynamic testing is not necessary for first line symptomatic management of lower urinary tract dysfunction, but post void residual urine determination is (1). This is in opposition to the general urological opinion, but urological consultation is as a rule difficult to obtain for the large numbers of MS patients. It needs to be pointed out that no prospective study has investigated the cost benefit of invasive urodynamics vs. simpler diagnostics (post void residual, upper urinary tract ultrasound). Thus, particularly for MS patients, the simple pragmatic approach can be advocated (6), and more invasive procedures are reserved for the patient with refractory problems.

In determining upper urinary tract dilatation ultrasound scanning has largely overtaken intravenous urography.

No definite study on the value/necessity of a particular battery of tests of urinary tract function in MS patients has been performed yet.

Management: The treatment of patients with MS is coordinated by the neurologist; same should hold for treatment of their urogenital symptoms, i.e., this treatment should also be coordinated by the neurologist or the neurorehabilitation physician. Referral to urology is often impractical for first line management, and neurological teams engage more and more in solving simple early urogenital problems themselves, and only refer to urology if first line treatment fails.

In managing MS patients with LUT dysfunction a specially educated nurse (''continence advisor'') is very helpful.

Treating LUT symptoms Some patients with hesitation, difficulty in initiating voiding and poor emptying may stimulate their bladder by suprapubic vibration. A practical device is commercially available (1).

Scheduled voiding (bladder training) may be an adequate treatment for patients with mild symptoms of frequency and urgency, or hyposensitive bladders. Complete and regular emptying of the bladder may be all that is necessary to alleviate frequency, urgency, incontinence and bladder discomfort.

If bladder training and scheduled voiding do not suffice, a simple algorithm for the management of frequency, urgency and incontinence can be followed: clean intermittent catheterisation should be introduced if the value of the post void residual is above 100 ml; if symptoms persist, an anticholinergic drug should be added. More selective muscarinic antagonists may be preferable if dry mouth or cognitive side effects occur (dariphenacine, soliphenacine).

Clean intermittent selfcatheterisations may become necessary after introduction of the anticholinergic drug because of appearance of significant residual urine is a side effect of the drug treatment (1).

In patients with post void residual urine above 100 ml the bladder should be regularly emptied by clean intermittent self catheterisation. This can be achieved by the patient or sometimes by the caregiver. Motivation, cognition and adequate manual dexterity are necessary conditions.

In patients with bothersome day or night time frequency desmopresine has been shown to be of symptomatic benefit providing patients with up to 6 hours of freedom from frequency (15). Desmopresine in a dose of 10–20 μg should only be used once in any 24 hours period; it should not be used regularly because of the danger of hyponatremia; it should not be used in patients over 65-years of age.

Patients with resistant neurogenic detrusor overactivity should be referred to an urologist interested in treating neurological patients. Botulinum toxin infiltration of detrusor has been shown to be effective in treating frequency, urgency and urgency incontinence. The beneficial effects of this therapy have a median duration of 13 months. Many patients need to start intermittent self catheterisation after botulinum injections (due to the inability of the detrusor to empty the bladder) (16). It is necessary to note that botulinum toxin A is not yet licensed for the use in bladder.

Intrasphincteric injections of botulinum toxin may improve urinary retention, but this type of therapy is still investigational (17).

Further therapies are being explored. It has been known for several decades that electrical stimulation can inhibit the overactive detrusor (also in patients with multiple sclerosis), but only uncontrolled and small studies have confirmed the efficacy of such therapy. Electrical stimulation can be applied by surface electrodes placed in the lumbosacral dermatomes, or by intravaginal or intrarectal electrode plugs (18). The invasive and much more expensive sacral nerve neuromodulation has been reported as inducing clinical and urodynamic improvement at 46 months follow up in MS patients (19). Recently repetitive transcranial magnetic stimulation of the motor cortex for 5 consecutive days over 2 weeks in MS patients complaining of lower urinary tract symptoms has been demonstrated to ameliorate the voiding phase of the micturition cycle (20).

Treating LUT infections Urinary tract infections are common symptoms of lower urinary tract dysfunction in MS patients, usually caused by incomplete emptying. They should be treated aggressively as they aggravate weakness, spasticity and may even

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foster new inflammatory activity and relapses of MS. Optimal treatment of retention is primarily important; intermittent selfcatheterisation to completely empty the bladder on a regularly basis may have to be instituted. If urinary tract infections continue an urologic evaluation is warranted to look for foreign bodies or bladder deformities (kidney and bladder stones are particularly common since certain types of bacteria my cause them). Chronic antibiotic use should be discouraged; this practice will almost certainly lead to infections with resistant bacteria. The strategy is to use intermittent or alternating courses of antibiotics (nitrofurantoin or trimethoprine). In patients with indwelling catheters asymptomatic bacteriuria should be expected and tolerated.

Treating LUT dysfunction in advanced MS In the highly disabled MS patient with limited mobility, cognitive impairment, loss of manual dexterity and increased spasticity clean intermittent self catheterisation (even with the aid of the caregiver) may become difficult, and an indwelling catheter becomes a necessity. Usually a urethral catheter connected to a leg bag is introduced first but should be promptly replaced by a suprapubic catheter (1). Use of urethral catheters on a long term basis causes urethral trauma and several other complications. The suprapubic catheter is as a rule introduced by the urologist. The catheter tract becomes epitelised in 6–8 weeks post-puncture; at that point the catheter can be changed for the first time and than subsequently at 3-month intervals (the regular change of catheter can be performed by a nurse).

Upper urinary tract complications such as hydronephrosis, reflux and pyelonephritis have been reported in up to 19% of 180 patients (21); several other studies reported lower incidence of these serious complications. An indwelling catheter *per se* does not protect the upper urinary tract. In advanced multiple sclerosis repeated post void residual urine measurements and ultrasound of kidneys and bladder are necessary. It has been stressed that management in advanced MS is based on tradition rather than on evidence (22). Permanent catheterisation is the method of choice for treating urinary problems in advanced MS, but the long term consequences are often neglected (catheter blockage, stones, infection; long term catheterisation is risk factor for developing bladder cancer). Haematuria is to be considered as a warning sign that must lead to further investigation.

Sexual Dysfunction

Introduction: Sexual excitement and satisfaction from adequate stimuli are a normal component of a fulfilled life. To the neurologist, sexual behavior involves a series of neurally controlled phenomena occurring in a hormonally defined milieu. Sexuality depends also on psychosocial factors, but the neurologist's interest is necessarily focused more on physiological aspects; nevertheless, the perspective of partnership and social issues should not be forgotten.

Sexual dysfunction, such as lack of libido (in both sexes), erectile dysfunction and disturbances of ejaculation (in men), and deficient lubrication, dyspareunia, and problems with orgasm (in women), is not uncommon in the general population (23), but much more common in MS (24). Sexual functioning needs to be addressed in patients since it is a major determinant of quality of life, and may be responsive to treatment.

Neurophysiology of the sexual response: Any lesion involving neural tissue relevant for sexual responses may cause dysfunction, as also may lesions of other neural structures more generally involved in control of behaviour. Thus, forebrain areas regulate the initiation and the execution of sexual behavior; the medial preoptic area integrates sensory and hormonal signals, and the amygdala and other nuclei play a role in the execution and reward aspects of sexual function. Desire or sexual interest (libido) is enhanced by sexual activity itself, exciting circumstances, new sexual partners, hypomania, and certain focal brain lesions (particularly of the frontal and temporal lobes). Sexual interest may be lowered by lack of opportunity, age, certain addictive or sedative drugs, malnutrition, debilitating illness, depression, and certain focal brain lesions.

Sexual excitement results from sensory stimuli or sexual ideation. Sensory information from the glans and the skin of the penis and clitoris is conveyed through bilateral branches of the pudendal nerve (the dorsal nerves of penis/clitoris). Genital afferents synapse in the spinal cord via interneurons with both somatic and autonomic motoneurons; those afferents destined for supraspinal structures travel in the anterolateral funiculus. ''Erotically colored'' sensations from the genital region are conveyed by the spinothalamic pathways, and patients with selective damage to these tracts may complain of anorgasmia and ejaculatory failure. Orgasmic sensation is blocked by bilateral anterolateral lesions of the spinal cord (25). Both thalamic and cortical areas receive sensory input from the genitals. Somatosensory input from other body parts (''erogenic zones'') may – subject to somatic and individual psychological factors and dependent on context – also lead to sexual excitement. Adequate sexual excitation can be achieved by stimuli delivered through cranial nerves, and mental imagery.

Sexual excitement leads to a complex response of the autonomic nervous system, and a particular behavioral response. Blood flow in the penile artery, or the corresponding artery in the clitoris, increases. The smooth muscle of the cavernosal sinuses in the penile corpora relax, and the helicine arterioles branching from cavernosal arteries selectively shunt blood flow to the lacunar spaces of the cavernosal bodies, filling them with blood. Subtunical venules are compressed so that corporeal venous return is restricted, resulting in increasing intracorporeal pressure. The pressure stabilizes at approximately systolic blood pressure, resulting in penile (and clitoral) tumescence and rigidity. Continued sacral parasympathetic activity maintains this erection (26). In women, parasympathetic activity causes clitoral erection, engorgement of the labia, and vaginal lubrication. The lubrication during sexual arousal is due to transudation through the vaginal wall. Another source is secretion from paraurethral glands (emptying into the urethra). Increased vaginal blood flow, lubrication, and erection of cavernous tissue in the clitoris and around the outer part of the vagina are the female homologues of the male erectile response; the response is dependent on innervation and a normal estrogen level (27). In the periphery, the main proerectile transmitter is nitric oxide, which is co-localized with vasoactive intestinal peptide and acetylcholine; the main antierectile neurotransmitter is norepinephrine (28). Erections can still occur in men after lesions of sacral cord and pelvic nerves. This is due to the ''alternative'' proerectile sympathetic pathway mediated through the thoracolumbar cord and the hypogastric nerve. The ''reflex''–''psychogenic'' dichotomy of the genital sexual response can be seen in both genders (29).

Orgasm can be separated conceptually (but not easily physiologically) from emission and ejaculation. Anorgasmia is very rare in otherwise normal men (30), but 13 percent of women between the ages of 18–26 years have never achieved orgasm, with the incidence declining to a minimum of 3 percent in women between the ages of 51 and 64 years (31).

Physiological inhibitory influences on the sexual response also exist. A center in the rostral ventral medulla (in the region of nucleus paragigantocellularis) seems to mediate tonic inhibition of sexual reflexes by a direct serotoninergic pathway descending to spinal centers (32).

Sexual dysfunction due to MS: Disturbances of sexual function are common in patients with multiple sclerosis, regardless of gender (25). Most such disturbances seem to relate to spinal cord involvement by the disease and are often associated with urinary symptoms and lower limb involvement. Sexual dysfunction has also been correlated with destructive lesions in the pons, as

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detected by magnetic resonance imaging, in patients with relapsing–remitting multiple sclerosis (33).

Changes in sexual function are rare at the onset of multiple sclerosis. Erectile dysfunction may be an initial symptom (34), and it becomes more common with increasing spinal cord involvement. In men with established MS it is a frequent problem, with estimates of its prevalence varying between 35 and 80 percent (35). Interest in resuming sexual activity persists in 75 percent of patients (36). Spontaneous improvement in erectile function sometimes occurs.

In men with multiple sclerosis problems with ejaculation are also frequent (37,38) and are often coupled to the erectile dysfunction. Anorgasmia has been correlated with evidence on magnetic resonance imaging of brainstem and corticospinal abnormalities as well as with total area of lesions (39).

In women, decreased lubrication and sensory disturbances involving the genital region (hypoesthesia, hyperesthesia, and different types of pain) are common (40). Sacral-segment dysesthesias may be so severe that patients are unable to bear direct genital or non-genital contact. Electrodiagnostic data – cortical evoked potentials of the dorsal nerve of the clitoris (41) – as well as measurement of vibratory thresholds in the clitoris (42) suggest that pudendal somatosensory input is necessary for female orgasmic function, and that this may be disturbed even in early, mild multiple sclerosis. To compensate for such a loss, more direct stimulation of the anterior vaginal wall is recommended.

Some patients with multiple sclerosis experience decreased libido; this problem has not been studied in depth, however, and emotional and cognitive disturbances may be contributory. Increased sexual desire occasionally constitutes a problem. Other symptoms related to multiple sclerosis, such as fatigue, depression, cognitive dysfunction, spasticity in the lower limbs, urinary and bowel disturbances, and the use of aids to manage incontinence, can inhibit sexuality, as can paroxysmal motor and sensory disturbances triggered by sexual intercourse.

Examination: The breadth of the history and clinical examination will be tailored by the individual physician's interests and practice habits; inquiry about sexual function should, however, be obligatory and not reserved for the male patient. The history should include details of patient's sexual expectations, needs, and behavior. Before diagnosing dysfunction of sexual organs, the level of actual desire should be established. Men should be asked about erectile function (the occurrence of nocturnal erections, morning erections, and erections evoked by genital, visual, auditory, or psychogenic stimuli), and women about vaginal lubrication. The nature of ejaculation should be determined. Finally it should be clarified whether the patient can achieve orgasm. In some circumstances it may be helpful to interview the patient's partner. Formal questionnaires can be used to obtain standardized information on male sexual function (43). These questionnaires mostly focus on erectile dysfunction (the persistent inability to develop and maintain an erection sufficient for satisfactory sexual activity) (44). The impact on quality of life is covered by another inventory (45). Questionnaires have also been formulated to assess sexual function in women, for instance the female sexual function index (46). Formal questionnaires are not necessary for assessment of individual patients (47). Clinical examination contributes little to clarification of neurogenic sexual dysfunction, but defines the extent of other deficits due to MS, which may be relevant for sexual counseling (spasticity, sensory loss). Sexual or neurophysiological function tests have no major role in clinical practice; abnormalities can be demonstrated, but they do not, as a rule, influence decisions on therapy. In a study of women with multiple sclerosis, for instance, latency of pudendal (and tibial) somatosensory evoked potentials failed to predict the extent of sexual dysfunction (48).

Management: Sexual dysfunction associated with neurological disease often increases patients' distress. Discussion with patients and partners about their sexual life should be part of any rehabilitation strategy. In all instances, drug regimens should be reviewed for possible effects on sexual function. Sexual education, counseling, and specific suggestions about therapeutic methods are important, and should be provided by the treating physician.

The development of drug treatments by the oral and intracavernous routes has revolutionized the outlook for men with erectile failure.

Specific phosphodiesterase-5 inhibitors have been developed to treat erectile dysfunction, the first being sildenafil, which has now been used by several million men. The selective inhibitors of type 5 cyclic guanosine monophosphate phosphodiesterase augment the nitric oxide–mediated relaxation pathway in penile tissues by increasing available cyclic guanosine monophosphate in the corpus cavernosum. These medications therefore do not cause erection but enhance the response to sexual arousal. Sildenafil is an effective treatment for erectile dysfunction in men with multiple sclerosis (36). Sildenafil (25, 50, or 100 mg) is taken orally 1 hour before intended sexual activity. (Significant effects have been reported between 30 minutes and 4–6 hours after taking the medication.) Treatment should be begun with 25 mg or 50 mg, and the same dose taken several times before it is increased. Dose-finding studies have demonstrated a dose–response curve. Sildenafil can be used repeatedly, and if used once or twice per week there should be no fear of tachyphylaxis (49). Other phosphodiesterase inhibitors probably have similar effects also in MS men, although no formal studies have been performed.

The most common adverse events of sildenafil are headache, flushing, and dyspepsia. Temporary visual symptoms (mainly color-vision disturbances) may occur with higher doses (100 mg). Adverse effects are mostly transitory and of minor intensity. No evidence was found of effects on the myocardium or the conduction system. Evaluation of functional capacity is necessary in patients with coronary artery disease, who need to know the risks of physical (and sexual) activity. Patients who can exercise to 4.5 metabolic equivalents without angina or hypotension can probably safely use sildenafil (50). Recommendations for the use of sildenafil in patients with cardiovascular disease have been published (50).

Phosphodiesterase-5 inhibitors are contraindicated in combination with vasodilator drugs of the nitro type and nitric oxide donors, but a cardiologist can change such drug regimens in suitable patients with erectile difficulties requiring treatment. Phosphodiesterase-5 inhibitors should not be used in patients with retinitis pigmentosa. They are contraindicated in men with hypotension (blood pressure below 90/50 mmHg). Intrapenile injections of papaverine have been used in the treatment of erectile dysfunction in men with multiple sclerosis (51) and other neurogenic conditions. The required dosage of papaverine was lower than in vascular disease, and erection lasted longer and was of better quality. Priapism and prolonged erection were the most common acute complications but were dose related. Prostaglandin E1 (alprostadil) is now the preferred drug for self-injection therapy in erectile dysfunction. Intracavernous injection should be taught under medical supervision before self-administration is attempted by the patient or his partner. The effect is very rapid and may last for 2–4 hours. Local bleeding, pain and fibrosis may develop in the corpora cavernosa, leading to loss of effectiveness. This treatment is obviously contraindicated in patients taking anticoagulants or with hematological malignancies. Priapism as an adverse drug reaction usually has a good prognosis with conservative treatment. Painless priapism of less than 6 hours duration should be treated at first by cooling (52). If present for more than 6 but less than 24 hours, intracavernous injection of an alpha-adrenergic agonist such as metaraminol is recommended. In painful priapism or with failure of conservative methods, penile puncture should be performed, at which time a cavernosal blood sample should be obtained to assess cavernosal hypoxia.

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A vacuum device can provide rigidity adequate for sexual intercourse (penetration) in a high percentage of patients, but many find it inconvenient. The most common complications are bruises, petechiae, and skin edema. The constriction band should not stay in place for longer than 30 minutes; major complications such as severe erosion, and cellulitis have been associated with prolonged wearing of the band (53). The use of a constriction band (on its own) may help patients who can obtain an erection, albeit not a durable one; the same restrictions concerning the duration of application should be observed.

In cases of anejaculation/anorgasmia, vibratory stimulation may be helpful.

Premature (or rapid) ejaculation has been associated with myelopathy, but also with behavioral, psychological, and partner-related issues. Counseling on the use of particular techniques may lead to improvement (54). Use of antidepressants (serotoninergic agents such as clomipramine, or selective serotonin reuptake inhibitors such as sertraline or paroxetine) may be successful (55).

Vibratory stimulation and dildos may be helpful in patients with genital sensory disturbances. Treatment of lack of sexual arousal and anorgasmia in women is difficult; no drug treatment is effective. Sildenafil has been well tolerated in women with lack of sexual arousal and multiple sclerosis, with few benefits or side effects. There was an effect on lubrication, but quality of life did not improve significantly although some women opted to continue on the drug after conclusion of the study (48). In women with dysesthetic or painful sensations in the genitalia that are not alleviated by improving lubrication, antiepileptic drugs such as gabapentin, pregabalin, and carbamazepine may be helpful.

Conclusion: Urogenital dysfunction is common in MS patients and should be looked for, as patients may hesitate to offer information. Looking after MS patients in a MS centre with a specialised nurse provides a good solution for early detection and appropriate counseling. Diagnostics should be coordinated by the neurologist. In sexual dysfunction as a rule no further diagnostics is necessary. In patients with LUT dysfunction simple measurement of post void residual urine (preferably by the specialised nurse in the MS center) along with analysis of a voiding diary may suffice for first line treatment – symptom oriented management. Providing for proper bladder emptying is of paramount importance for alleviating symptoms and preventing infections. Ideally, the MS center would cooperate with an interested urologist, to whom complex cases should be referred.

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Immunotherapy of multiple sclerosis

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Abstract: Multiple sclerosis (MS) is regarded as a prototypic inflammatory autoimmune central nervous system disorder causing neurological disability in young adults. Recommended basic immunomodulatory therapies of MS are currently interferon beta and glatiramer acetate. Both have proven to be clinically and paraclinically effective and clinical evidence suggests that treatment should be initiated as early as possible.

However, despite the fact that therapeutic options for MS have significantly been widened over the past decade there is still tremendous activity in the search for new treatment options for MS.

One important development in the field is reflected by the substantial number of promising results for oral therapies. Various phase III clinical trials are currently being initiated or are already underway evaluating the efficacy of a variety of orally administered agents, including cladribine, teriflunomide, laquinimod, fingolimod and fumaric acid. It is hoped that these oral therapies for MS further broaden our armament for MS therapy.

Introduction: Multiple sclerosis (MS) is the most common neurological cause of disability in young adults with a lifetime risk of one in 400. MS is considered as an autoimmune inflammatory disorder of the central nervous system (CNS) which is influenced by environmental factors and susceptibility genes (1,2). Both temporal and spatial dissemination of lesions in the CNS is needed to clinically diagnose MS. The risk for developing clinically definite MS (CDMS) is highest when asymptomatic white-matter lesions in the brain can be found by MRI (3). But also patients with an isolated clinical deficit as for example optic neuritis (clinically isolated syndrome; CIS) are at risk of developing MS in the course of time. In one follow-up study, the 10-year risk of developing CDMS was 39%, the 20-year risk was 49%, the 30-year risk was 54% and the 40-year risk was 60% (4). The diagnostic criteria for MS (McDonald criteria) take these findings into consideration and allow diagnosing MS even before a second clinical event. Instead MRI evidence of dissemination of CNS lesions in time and space is sufficient for the diagnosis of MS (5,6). The presence of oligoclonal bands doubles the risk for having a second attack while not influencing the development of disability (7).

In the course of years, the majority of MS patients develop progressive neurological disabilities. About 50% of MS patients will use a cane to support walking within 10 years and the disease course of most MS patients will develop into a secondary progressive form of the disease displaying substantial residual clinical deficits (8,9). The disease activity in early phases of the

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