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REVIEW

Multiple sclerosis and sexual dysfunction

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder of the central nervous system characterized by episodic and progressive neurologic dysfunction resulting from inflammatory and autoimmune reactions. The underlying pathogenesis of MS remains largely unclear. However, it is currently accepted as a T cell-mediated autoimmune disease. Among other clinical manifestations, sexual dysfunction (SD) is a painful but still underreported and underdiagnosed symptom of the disorder. SD in MS patients may result from a complex set of conditions and may be associated with multiple anatomic, physiologic, biologic, medical and psychological factors. SD arises primarily from lesions affecting the neural pathways involved in physiologic function. In addition, psychological factors, the side effects of medications and physical symptoms such as fatigue, muscular weakness, menstrual changes, pain and concerns about bladder and bowel incontinence may also be involved. Since MS primarily affects young people, SD secondary to MS may have a great impact on quality of life. Thus, maintaining a healthy sexual life with MS is an important priority. The treatment of SD requires multidisciplinary teamwork and cooperation among specialists, individual patients, partners and the society.
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INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disorder of the central nervous system (CNS) characterized by episodic and progressive neurologic dysfunction resulting from inflammatory and autoimmune reactions.[1] The onset of MS mainly occurs in younger persons between the ages of 20 and 40 years, and the symptoms are usually complex and have a great impact on patients' quality of life (QoL).[2] Among other clinical manifestations, sexual dysfunction (SD) is a painful but still underreported and underdiagnosed complication of MS. Therefore, a comprehensive understanding of SD secondary to MS is important.

MS: AN AUTOIMMUNE DISORDER OF THE CNS

Pathogenesis of MS

MS occurs as a result of some combination of genetic, environmental and infectious factors; the disorder may also involve other factors such as vascular problems.[3] The most widely accepted hypothesis for MS pathogenesis is an autoimmune mechanism.[4–6] In the CNS, immune cells cause myelin and axonal damage, and consequently, result in variable loss of neurologic functions.[7] In the brains of MS patients, these promyelinating neurosteroidal functions are impaired; hence, Leitner[8] proposed a new hypothesis, suggesting that a deficiency of neurosteroids such as progesterone in the CNS leads to dysmyelination characterized by an altered myelin protein composition, which may play a decisive role in the pathogenesis of MS.

Clinical subtypes of MS and the McDonald criteria for the diagnosis of MS

MS can be divided into four clinical subtypes: relapsing–remitting MS (RRMS), secondary progressive MS, primary progressive MS and progressive relapsing MS (**Figure 1**).[4,9] Later, clinically isolated syndrome was recognized; this syndrome refers to the first attack of MS.[10,11] The McDonald criteria for MS diagnosis were introduced in 2001,[12] and have experienced two major revisions, i.e., in 2005 and 2010, respectively.[13,14] The 2010 revision simplified and speeded diagnosis, howbeit maintaining adequate sensitivity and specificity.[15]

MS AND ENDOCRINE DISORDERS

Endocrine disorders have been found in MS. Although the pathogenesis is poorly understood, both the hypothalamic–pituitary–adrenal (HPA) axis and the hypothalamic–pituitary–gonadal (HPG) axis might be implicated.

The HPA axis

The HPA axis plays an important role in the control of the disease process in MS. In 1994, Michelson *et al.*[15] found elevated basal plasma levels of cortisol, adrenocorticotropic hormone and adrenals in MS patients,[16] Huitinga *et al.*[17] observed a pronounced activation of corticotropin-releasing hormone neurons and increased cortisol in the cerebrospinal fluid of MS patients; these findings indicate the activation of the HPA axis. Ysrraelit *et al.*[18] studied 173 patients with MS and found that all patients displayed higher concentrations of cortisol, adrenocorticotropic hormone and dehydroepiandrosterone sulfate in plasma than controls, suggesting HPA hyperactivity. Later, Huitinga *et al.*[19] found that the more active MS lesions were present in the hypothalamus, the shorter the disease duration was until the moment of death.

The HPG axis

Various types of inflammation are known to disrupt the HPG axis and to interfere with gonadal hormone production and reproductive function.[20]

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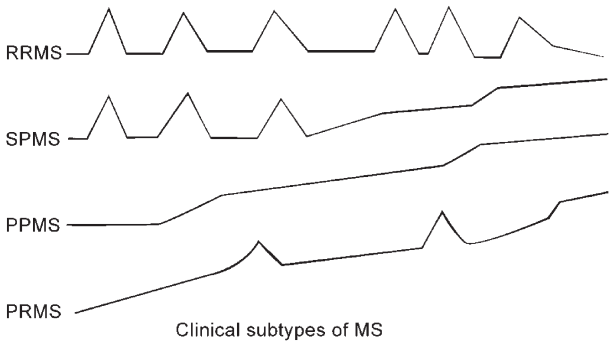

Figure 1 The four common subtypes of MS according to the clinical course. RRMS: at least one clinical attack results from demyelination (relapsing phase), followed by complete or partial recovery (remitting phase). SPMS: neurologic deficits are continuously and gradually worsening, after a period of RRMS. PPMS: symptoms continue to worsen after the onset of the disease, without an apparent relapsing–remitting turnover. PRMS: MS with features of both PPMS and RRMS. MS, multiple sclerosis; PPMS, primary progressive MS; PRMS, progressive relapsing MS; RRMS, relapsing–remitting MS; SPMS, secondary progressive MS.

The pathophysiology of MS is complex, with demyelination and axonal degeneration contributing to inflammatory neurodegenerative processes.[21] Sex steroids have a trophic, maturation-stimulating, and survival-promoting role for neurons in the developing and, presumably, adult brains.[21] Progesterone derivatives seem to act as promyelinating factors in the slow, but continuous process of myelin maintenance. Estradiol induces the transcription of progesterone receptors while stimulating *de novo* synthesis of neuroprogesterone by astrocytes in the brain.[22] Both estrogen and progesterone can directly protect neurons from apoptosis by interfering with intracellular cell death cascades.[21] Clinical data point to a disturbance of steroid hormone metabolism in MS. The disease itself can affect sex hormone levels, owing to damage in the hypothalamic regions, dysfunction of the HPG axis, or an altered metabolism.[21]

Gender may affect the susceptibility to and the course of MS; the disease has a greater prevalence and a better prognosis in women than in men.[23,24] The clinical course of MS in women is frequently related to the menstrual cycle. At the beginning of menstruation, when a lower level of progesterone is present, more frequent relapses or worsening of symptoms is observed in MS patients.[22,25] Multiple lines of evidence indicate that pregnancy is associated with attenuated clinical symptoms and a decreased relapse rate.[9,26,27] The prospective European Pregnancy in Multiple Sclerosis study of 227 pregnancies found that the relapse rate increased during the first 3 months post partum, after the drop in sex steroid levels. The rate of relapse was reduced during the last 3 months of pregnancy,[28] when the concentrations of estrogen (estradiol and estriol) and progesterone in the cerebrospinal fluid are higher. In addition, Simon *et al.*[29] found that low testosterone levels occur in approximately 50% of patients with MS (females 57% and males 44%). Low hormone levels are associated with increased disease activity. Safarinejad *et al.*[30] studied the hypothalamic–pituitary–testis axis of 68 male MS patients aged 18 years or older and found that the total sperm count, sperm motility and percentage of sperm with normal morphology were lower in MS patients when compared with controls. They explained that the demyelination process and cytokines may alter the hypothalamic–pituitary–testis axis and testicular functions, resulting in low levels of serum sex hormones.[30] Tomassini *et al.*[31] found lower levels of serum testosterone in women with MS than in controls. Women with the lowest testosterone concentrations had more brain lesions detected by magnetic resonance imaging (MRI). Furthermore, a positive correlation was observed between testosterone concentrations and both tissue damage on MRI and clinical disability.[31] In men, higher estradiol levels were associated with a greater degree of brain tissue damage revealed by the extent of T2 hyperintense and T1 hypointense lesions.[31] Interestingly, sex steroid supplementation might be beneficial for MS patients. Both anti-inflammatory actions on the immune system or CNS and direct neuroprotective properties might be implicated.[32,33]

MS-ASSOCIATED SD

The sexual response cycle

The normal male sexual response cycle can be divided into *libido* (or sexual desire), erection, ejaculation, orgasm and detumescence (**Figure 2**).[34–36] The female sexual response cycle, which follows a pattern similar to that in men, has four main elements: *libido*, arousal, orgasm and satisfaction.[37] The integrity of the sexual response cycle is essential to human sexual response and functioning; any damage may result in SD.[37]

SD in the general population

In 1992, the National Health and Social Life Survey, which included 1410 men aged 18–59 years throughout the United States, revealed that the prevalence of any form of SD in men was 31%, with 'climaxing' or 'ejaculating too rapidly' the most commonly reported form of dysfunction.[38,39] The Global Survey of Sexual Attitudes and Behavior represented a collection of data from more than 27 000 men and women aged 40–80 years, in which 'early ejaculation' was the most commonly reported SD in men occurring at a rate of 14%; this was followed by 'erectile difficulties', with an overall rate of 10%.[39,40]

In a cohort of 703 Viennese women, approximately 22% of the women reported low sexual desire; 35% reported arousal problems and 39% reported orgasmic difficulties. Sexual pain disorders were reported by 12.8% of the samples.[41] The National Health and Social Life Survey found that SD affected about 43% of women; the most common self-reported sexual problem was low desire (38.7%), followed by reduced arousal (26.1%) and orgasm difficulties (20.5%).[38,39]

MS is associated with higher incidence of SD

Chronic medical conditions, including MS, are frequently associated with SD.[42] MS has a detrimental impact on the sexuality of both men and women.[42] The most common complaints of SD in men with MS are erectile dysfunction (ED, 50%–75%), ejaculatory dysfunction and/or orgasmic dysfunction (50%), reduced *libido* (39%) and anorgasmia (37%).[42–45] The frequency of SD is higher in female MS patients in comparison to the general population, with about 40%–74% of female MS patients suffering from sexual problems.[42] The most frequently described SD in women are reduced *libido*, difficulty in achieving orgasm, reduction in the tactile sensations originating from the thigh and genital regions and vaginal dryness with consequent dyspareunia.[21,46,47] Zorzon *et al.*[48] found that anorgasmia or hyporgasmia (37.1%), decreased vaginal lubrication (35.7%) and reduced *libido* (31.4%) were more commonly reported by women with MS, and impotence or ED (63.2%), ejaculatory dysfunction and/or orgasmic dysfunction (50%) and reduced *libido* (39.5%) were most commonly reported by men. The symptoms and potential treatment strategies of SD are shown in **Table 1**.[35]

The pathogenesis of SD in MS is largely unclear. Postulated pathogeneses are illustrated in **Figure 3**. One well-accepted hypothesis is that SD arises from spinal cord damage due to autoimmune responses.[1,35] Recently, however, experts have suggested that SD in MS may be due not only to lesions affecting the neural pathways involved in physiologic

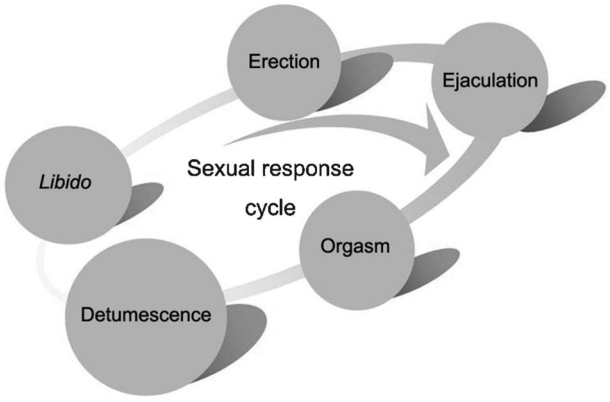

Figure 2 The normal male sexual response cycle can be divided into *libido* (or sexual desire), erection, ejaculation, orgasm and detumescence.

function, but also to psychological factors, the side effects of medications, physical symptoms such as fatigue, muscular weakness, changes in menses and pain, and concerns about bladder and bowel incontinence.[35] This is a complex set of conditions associated with multiple anatomic, physiologic, biologic, medical and psychological factors.[49]

Sex steroids play an essential role in modulating sexual function.[50] Estrogens play a vital role in the physiologic function of tissues throughout the body, including the CNS and lower genital tissues; androgens influence the development of female sexual function and represent the immediate precursors to estrogen.[50] They can affect sexual desire, mood, energy and well-being of patients.[8,50,51] Hormonal imbalances in MS have been reported in many studies.[15,16,20–22] Lombardi *et al.*[52] studied 55 women of reproductive age; 36.4% showed abnormal hormonal levels. In male patients with MS, ED and ED might be partially correlated to the reduced blood testosterone levels. Male MS patients with SD had abnormally low serum testosterone levels, ED and diminution in *libido*. After treatment with testosterone, sexual function was remarkably improved.[32,51]

Psychological factors are another important cause of SD. Janardhan *et al.*[53] investigated 60 subjects with MS and assessed their QoL in MS using the Multiple Sclerosis QoL-54 score and demonstrated that fatigue and depression were independently associated with an impaired QoL in MS. Marrie *et al.*[54] studied the mental comorbidity of 8983 patients with MS and reported that mental comorbidity affected 4264 (48%) responders. Depression was the most frequently comorbidity (4012, 46%), and additional depression was found among 16.2% of patients not reporting any mental comorbidity, suggesting that it is often undiagnosed and undertreated. Alshubaili AF assessed the QoL of 170 MS patients, including 145 (85.3%) with RRMS and 25 with secondary progressive MS; this study also found that depression was the most common significant covariate of QoL domains.[55]

In addition, the side effects of treatment for MS should be emphasized. One of the adverse effects of antidepressants is delayed orgasm or loss of orgasm response. Between 30% and 60% of patients treated with selective serotonin-reuptake inhibitors may experience some form of treatment-induced SD.[56] Selective serotonin-reuptake inhibitor-induced SD may be overcome with lowering doses, or by switching to an antidepressant with a low propensity to cause SD (bupropion, mirtazapine, nefazodone and reboxetine), or through the addition of 5-hydroxytryptamine receptor two antagonists (mirtazapine and mianserin).[57] Other antidepressants, such as bupropion, nefazodone and mirtazapine, are associated with SD to varying extents.[56] Some supportive treatments such as urinary catheters may also interfere with a patient's sex life.[35]

Studies have suggested that SD in MS reflects three levels of influence.[35] Primary SD directly affects the neural pathways for sexual functions (direct physical), e.g., genital sensations resulting from lesions in the spinal cord. Secondary SD plays a critical role in limiting sexual expression due to fatigue and physical limitations (indirect physical).[35] Fatigue is one of the most common and disabling symptoms in MS.[35] Sensory deficits are also very common in women (about 60%), and sensory symptoms from the trunk and genitals correlated with orgasmic quality.[58] Bladder and sexual problems are common among MS patients, even for those who have had MS for a relatively short period of time. Bladder and sexual functions share the same segments of autonomic control.[58] Other symptoms such as bladder dysfunction, including frequency, urgency, incontinence and obstructive symptoms with urinary retention, can also be observed in MS patients.[35] In addition, the effect of disability (measured by the expanded disability status scale, EDSS) cannot be ignored in secondary SD. Hutler *et al.*[58] found a significant correlation between lower EDSS scores and negative sexual changes such as decreased lubrication, disappearance of clitoral erections and decrease in orgasmic capacity and sensations in 47 women with MS. However, another study of 41 women with MS found that EDSS scores did not correlate to the female sexual function index.[59] Tertiary SD arises from the psychological, emotional or cultural effects of living that can interfere with sexual feelings and the sexual response.[35,42] The most prominent symptom is depression. The correlation found between SD and depression may partially explain the high frequency of SD in MS patients.[60] The potential factors that predispose MS patients to SD are shown in **Table 2**.[35]

Interestingly, studies using experimental autoimmune encephalomyelitis, an animal model of MS, showed that the function of penile erection was affected in experimental autoimmune encephalomyelitis, evidenced by ultrastructural pathologic changes of the penile cavernous tissue.[61] This finding indicated that changes of the penile cavernous tissue may be one of the important mechanisms of ED caused by MS. The International Index for Erectile Function in men and Female

Table 1 Therapies for various sexual dysfunction in multiple sclerosis

Dysfunction	*Symptoms*	*Treatment*
Sexual desire dysfunction	Decreased sexual desire or motivation	Sex steroids therapy (testosterone), psychotherapy
Sexual arousal dysfunction	Males: diminished feelings of sexual excitement and sexual pleasure and/or erectile dysfunction	Drugs: phosphodiesterase type 5 inhibitor, adrenoceptor antagonists, dopamine agonist, prostaglandin
	Females: diminished feelings of sexual excitement and sexual pleasure and/or vulval swelling	Drugs: Vaginal lubricants, sildenafil
Ejaculatory dysfunctions	Delayed or absent ejaculation	Drugs: Midodrine, yohimbine
Orgasmic dysfunctions	Diminished or absent orgasms	Availability of oral medication and a multidisciplinary teamwork and cooperation
Sexual pain disorder	Female dyspareunia	Anesthetic gels, pain modulation, specialist care

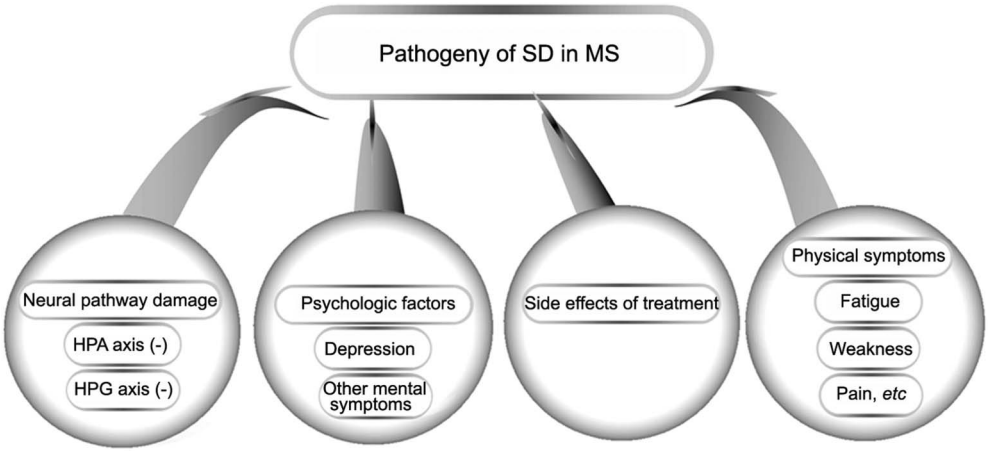

Figure 3 SD in MS patients can be owing to lesions affecting the neural pathways that are involved in physiologic function, among which the HPA axis and the HPG axis might be compromised. Psychological factors such as depression, side effects of medications and physical symptoms including fatigue and muscular weakness may contribute to the pathogenesis of SD in MS. (−) denotes compromising effects. HPA, hypothalamic–pituitary–adrenal; HPG, hypothalamic–pituitary–gonadal; MS, multiple sclerosis; SD, sexual dysfunction.

Sexual Function Index in women are helpful in assessing all sexual function domains and also in evaluating the impact of a specific treatment.[62] Pudendal somatosensory evoked potential testing is an emerging tool for evaluation of the genital somatosensory pathway disruption in MS-induced ED.[63]

TREATMENT OF SD IN MS

SD has a great impact on QoL,[2] and maintaining a healthy sexual life with MS is an important priority. The management of male SD has advanced considerably with the availability of oral medication, but therapeutic strategies in SD are still not satisfactorily established.[35,64]

Drug treatment for SD in MS

The first-line therapies for male SD are phosphodiesterase type 5 inhibitors. Fowler *et al.*[64] studied 217 men with MS and found that sildenafil treatment for ED in men with MS was effective and well tolerated. Tadalafil also proved effective in the treatment of ED in MS.[65] However, a study by Safarinejad indicated that sildenafil had little effect on MS-associated emergent ED when compared with a placebo.[66] Food, especially fatty food, which can affect the pharmacokinetic profiles of sildenafil may explain this discrepancy.[67] Dopamine agonists, e.g., apomorphine are also effective for MS patients with ED.[68] Alprostadil (prostaglandin E1) and adrenoceptor antagonists (phentolamine) have been proven useful (**Table 3**).[69,70] Priapism, a pathologic erection that lasts longer than 4 h despite lack of sexual stimulation, is a complication in patients treated with intracavernous (1%) or intraurethral (<1%) application of these vasoactive drugs. Patients should be informed of this complication and advised to seek treatment, if erection lasts longer than usual.[35] Dose titration during the initial stages was recommended to avoid priapism.[70] In contrast to the many therapeutic options available for men, drug treatment for women is limited. Dachille *et al.*[71] studied 97 women and 124 men with SD and revealed that sildenafil was effective and safe in the treatment of SD in both sexes. However, Dasgupta *et al.*[72] found that sildenafil only produces a limited benefit (such as an increase in vaginal lubrication) in some women with SD. Thus, this drug seems unlikely to help all female patients with neurogenic SD. Sildenafil citrate may also be effective in women with female sexual arousal disorder secondary to MS, diabetes or antidepressant use; however, more trials in these patient populations are required to confirm these findings.[73]

Recently, combination therapies have been adopted for more refractory cases of ED.[74] Published combination therapies include phosphodiesterase type 5 inhibitor plus vacuum erectile device, intraurethral medication, intracavernosal injection, androgen supplement, α-blocker or miscellaneous combinations.[74] Traditional Chinese medicine has long been used in treating SD of various etiologies.[75,76] More studies are warranted to explore the potentials of these combination therapies or herbal medicines for the management of MS-associated SD.

Table 2 Potential factors predisposing a multiple sclerosis patient to sexual dysfunction

Levels	*Factors*
Primary	Lesions affecting the neural pathways for sexual functions
Secondary	Effects of disability (muscle weakness, *etc.*)
	Fatigue
	Sensory deficit/dysesthesia/allodynia
	Difficulties in attention or concentration
	Incontinence
	Other factors
Tertiary	Psychological, emotional or cultural effects of living including:
	Depression and other emotional problems
	Altered self-image or low self-esteem
	Change in the relationship with the partner
	The side effects of drugs such as antidepressants, baclofen, *etc.*
	Use of urethral indwelling catheter

Hormone therapy

As mentioned previously, sex steroids play an essential role in modulating sexual function in both men and women. Most patients with MS have abnormal levels of sex steroids, so these steroids may serve as potential therapeutic agents for SD. Foster *et al.*[32] treated four male MS patients with SD who had abnormally low serum testosterone levels. After testosterone treatment, SD (both ED and diminution in *libido*) was improved. Further studies showed that sex steroids could protect the brain from demyelination and stimulate remyelination, which may be a new therapeutic tool for the treatment of MS.[33]

Table 3 Drugs used to treat male sexual dysfunction

Types	*Drugs*	*Mechanism*
Phosphodiesterase type 5 inhibitor	Sildenafil (Viagra) Vardenafil (Levitra) Tadalafil (Cialis)	Increase the cyclic guanosine monophosphate levels
Vasoactive drugs	Prostaglandin E1 (Caverject, Viridal)	Induce erection through smooth muscle relaxation
Dopamine agonist	Apomorphine (Uprima, Ixense)	Acting on the central nervous system
Adrenoceptor antagonists	Phentolamine Yohimbine	α-adrenoceptor activation

Psychotherapy

Psychotherapy for sexual problems requires multidisciplinary teamwork and cooperation among specialists, partners and society. It must be based on the belief that despite their disabilities, patients with MS are still sexual persons with the ability to share love, bonding, intimacy and sexual experiences.[42,54,74] Foley *et al*.[77] carried out a counselling intervention with nine couples utilizing a quasi-experimental research design, which resulted in marked improvements in affective and problem solving communication, marital satisfaction and sexual satisfaction.

Other approaches

For some patients with neurogenic ED, somatosensory disturbances might necessitate vibratory stimulation for achieving erection. Often, a simple, store-bought vibrator applied to the glans penis is sufficient to produce a satisfactory result. When the result is transient, or if rigidity is not sufficient for vaginal penetration, other agents can be used to augment the effect.[45] The vacuum erection device is another alternative in the management of neurogenic ED.[45]

Multidisciplinary approached to evaluation and management of SD in MS

Given the complexity and multifactorial nature of SD, a multidisciplinary approach to the evaluation and management of SD in patients with MS, incorporating the latest data from the fields of urology, neurology, nursing, social work and psychology, is necessary.[42,45] One of the approaches used in handling problems related to sexuality is the permission, limited information, specific suggestions and intensive therapy model.[35] It is a hierarchical approach to the management of SD that guides healthcare professionals in assessing the needs of patients and planning appropriate interventions.

CONCLUSIONS

SD in MS is a complex set of conditions, associated with multiple anatomic, physiologic, biologic, medical and psychological factors. SD has a great impact on QoL. The treatment of SD in MS requires multidisciplinary teamwork and cooperation among specialists, individual patients, partners and society. Phosphodiesterase type 5 inhibitors are first-line therapies for MS-associated ED in both male and female patients. If oral agents are ineffective, second-line treatments such as intracavernous or intraurethral application of prostaglandin E1 and third-line therapies, such as surgical implantation of a penile prosthesis or acuum erection device, may be indicated in male MS patients. For female patients, hormone therapies and psychotherapy may serve as important alternatives. Our review alerts the neurologists to the importance of paying more attention to the incidence of SD in MS patients.

AUTHOR CONTRIBUTIONS

ZNG and HLZ wrote the paper. ZNG and SYH carried out the literature review. HLZ, JW and YY reviewed the draft. All authors read and approved the final manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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1 Gauthier SA, Glanz BI, Mandel M, Weiner HL. A model for the comprehensive investigation of a chronic autoimmune disease: the multiple sclerosis CLIMB study. *Autoimmun Rev* 2006; **5**: 532–6.
2 Jønsson A. [Disseminated sclerosis and sexuality]. *Ugeskr Laeger* 2003; **165**: 2642–6. [Article in Danish].
3 Compston A, Coles A. Multiple sclerosis. *Lancet* 2008; **372**: 1502–17.
4 Zhang HL, Wu J, Zhu J. The immune-modulatory role of apolipoprotein E with emphasis on multiple sclerosis and experimental autoimmune encephalomyelitis. *Clin Dev Immunol* 2010; **2010**: 186813.
5 Stinissen P, Raus J, Zhang J. Autoimmune pathogenesis of multiple sclerosis: role of autoreactive T lymphocytes and new immunotherapeutic strategies. *Crit Rev Immunol* 1997; **17**: 33–75.
6 Fletcher JM, Lalor SJ, Sweeney CM, Tubridy N, Mills KH. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. *Clin Exp Immunol* 2010; **162**: 1–11.
7 O'Brien K, Gran B, Rostami A. T-cell based immunotherapy in experimental autoimmune encephalomyelitis and multiple sclerosis. *Immunotherapy* 2010; **2**: 99–115.
8 Leitner H. Influence of neurosteroids on the pathogenesis of multiple sclerosis. *Med Hypotheses* 2010; **75**: 229–34.
9 Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology* 1996; **46**: 907–11.
10 Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A *et al*. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 1997; **120**: 2059–69.
11 Tintoré M, Rovira A, Brieva L, Grivé E, Jardí R *et al*. Isolated demyelinating syndromes: comparison of CSF oligoclonal bands and different MR imaging criteria to predict conversion to CDMS. *Mult Scler* 2001; **7**: 359–63.
12 McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP *et al*. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001; **50**: 121–7.
13 Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP *et al*. Diagnostic criteria for multiple sclerosis: 2005 revisions to the 'McDonald Criteria'. *Ann Neurol* 2005; **58**: 840–6.
14 Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; **69**: 292–302.
15 Michelson D, Stone L, Galliven E, Magiakou MA, Chrousos GP *et al*. Multiple sclerosis is associated with alterations in hypothalamic–pituitary–adrenal axis function. *J Clin Endocrinol Metab* 1994; **79**: 848–53.
16 Reder AT, Makowiec RL, Lowy MT. Adrenal size is increased in multiple sclerosis. *Arch Neurol* 1994; **51**: 151–4.
17 Huitinga I, Erkut ZA, van Beurden D, Swaab DF. The hypothalamo–pituitary–adrenal axis in multiple sclerosis. *Ann NY Acad Sci* 2003; **992**: 118–28.
18 Ysrraelit MC, Gaitán MI, Lopez AS, Correale J. Impaired hypothalamic–pituitary–adrenal axis activity in patients with multiple sclerosis. *Neurology* 2008; **71**: 1948–54.

19 Huitinga I, Erkut ZA, van Beurden D, Swaab DF. Impaired hypothalamus–pituitary–adrenal axis activity and more severe multiple sclerosis with hypothalamic lesions. *Ann Neurol* 2004; **55**: 37–45.
20 Cavalla P, Rovei V, Masera S, Vercellino M, Massobrio M *et al*. Fertility in patients with multiple sclerosis: current knowledge and future perspectives. *Neurol Sci* 2006; **27**: 231–9.
21 Kipp M, Berger K, Clarner T, Dang J, Beyer C. Sex steroids control neuroinflammatory processes in the brain: relevance for acute ischemia and degenerative demyelination. *J Neuroendocrinol* 2012; **24**: 62–70.
22 Micevych P, Sinchak K. Estradiol regulation of progesterone synthesis in the brain. *Mol Cell Endocrinol* 2008; **290**: 44–50.
23 Greer JM, McCombe PA. Role of gender in multiple sclerosis: clinical effects and potential molecular mechanisms. *J Neuroimmunol* 2011; **234**: 7–18.
24 Jobin C, Larochelle C, Parpal H, Coyle PK, Duquette P. Gender issues in multiple sclerosis: an update. *Womens Health (Lond Engl)* 2010; **6**: 797–820.
25 Voumvourakis KI, Tsiodras S, Kitsos DK, Stamboulis E. Gender hormones: role in the pathogenesis of central nervous system disease and demyelination. *Curr Neurovasc Res* 2008; **5**: 224–35.
26 Elenkov IJ, Wilder RL, Bakalov VK, Link AA, Dimitrov MA *et al*. IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum: implications for autoimmune disease activity during these times. *J Clin Endocrinol Metab* 2001; **86**: 4933–8.
27 Hirabayashi Y. Cerebrospinal fluid progesterone in pregnant women. *Br J Anaesth* 1995; **75**: 683–7.
28 Vukusic S, Hutchinson M, Hours M, Moreau T, Cortinovis-Tourniaire P *et al*. Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. *Brain* 2004; **127**: 1353–60.
29 Simon EV, Topalli I, Touray A, Sadiq SA. Decreased serum testosterone levels in multiple sclerosis. *Neurology* 2006; **66**: A225.
30 Safarinejad MR. Evaluation of endocrine profile, hypothalamic–pituitary–testis axis and semen quality in multiple sclerosis. *J Neuroendocrinol* 2008; **20**: 1368–75.
31 Tomassini V, Onesti E, Mainero C, Giugni E, Paolillo A *et al*. Sex hormones modulate brain damage in multiple sclerosis: MRI evidence. *J Neurol Neurosurg Psychiatry* 2005; **76**: 272–5.
32 Foster SC, Daniels C, Bourdette DN, Bebo BF Jr. Dysregulation of the hypothalamic–pituitary–gonadal axis in experimental autoimmune encephalomyelitis and multiple sclerosis. *J Neuroimmunol* 2003; **140**: 78–87.
33 Acs P, Kipp M, Norkute A, Johann S, Clarner T *et al*. 17beta-estradiol and progesterone prevent cuprizone provoked demyelination of corpus callosum in male mice. *Glia* 2009; **57**: 807–14.
34 Kandeel FR, Koussa VK, Swerdloff RS. Male sexual function and its disorders: physiology, pathophysiology, clinical investigation, and treatment. *Endocr Rev* 2001; **22**: 342–88.
35 Kessler TM, Fowler CJ, Panicker JN. Sexual dysfunction in multiple sclerosis. *Expert Rev Neurother* 2009; **9**: 341–50.
36 Lue TF. Erectile dysfunction. *N Engl J Med* 2000; **342**: 1802–13.
37 Ho CC, Singam P, Hong GE, Zainuddin ZM. Male sexual dysfunction in Asia. *Asian J Androl* 2011; **13**: 537–42.
38 Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999; **281**: 537–44.
39 Derogatis LR, Burnett AL. The epidemiology of sexual dysfunctions. *J Sex Med* 2008; **5**: 289–300.
40 Nicolosi A, Laumann EO, Glasser DB, Moreira ED Jr, Paik A *et al*. Sexual behavior and sexual dysfunctions after age 40: the global study of sexual attitudes and behaviors. *Urology* 2004; **64**: 991–7.
41 Ponholzer A, Roehlich M, Racz U, Temml C, Madersbacher S. Female sexual dysfunction in a healthy Austrian cohort: prevalence and risk factors. *Eur Urol* 2005; **47**: 366–74.
42 Bronner G, Elran E, Golomb J, Korczyn AD. Female sexuality in multiple sclerosis: the multidimensional nature of the problem and the intervention. *Acta Neurol Scand* 2010; **121**: 289–301.
43 Redelman MJ. Sexual difficulties for persons with multiple sclerosis in New South Wales, Australia. *Int J Rehabil Res* 2009; **32**: 337–47.
44 Schmidt EZ, Hofmann P, Niederwieser G, Kapfhammer HP, Bonelli RM. Sexuality in multiple sclerosis. *J Neural Transm* 2005; **112**: 1201–11.
45 Fletcher SG, Castro-Borrero W, Remington G, Treadaway K, Lemack GE *et al*. Sexual dysfunction in patients with multiple sclerosis: a multidisciplinary approach to evaluation and management. *Nat Clin Pract Urol* 2009; **6**: 96–107.
46 Borello-France D, Leng W, O'Leary M, Xavier M, Erickson J *et al*. Bladder and sexual function among women with multiple sclerosis. *Mult Scler* 2004; **10**: 455–61.
47 Demirkiran M, Sarica Y, Uguz S, Yerdelen D, Aslan K. Multiple sclerosis patients with and without sexual dysfunction: are there any differences? *Mult Scler* 2006; **12**: 209–14.
48 Zorzon M, Zivadinov R, Bosco A, Bragadin LM, Moretti R *et al*. Sexual dysfunction in multiple sclerosis: a case–control study. I. Frequency and comparison of groups. *Mult Scler* 1999; **5**: 418–27.
49 Anastasiadis AG, Davis AR, Salomon L, Burchardt M, Shabsigh R. Hormonal factors in female sexual dysfunction. *Curr Opin Urol* 2002; **12**: 503–7.
50 Goldstein I, Traish A, Kim N, Munarriz R. The role of sex steroid hormones in female sexual function and dysfunction. *Clin Obstet Gynecol* 2004; **47**: 471–84.
51 Mikhail N. Does testosterone have a role in erectile function? *Am J Med* 2006; **119**: 373–82.
52 Lombardi G, Celso M, Bartelli M, Cilotti A, Del Popolo G. Female sexual dysfunction and hormonal status in multiple sclerosis patients. *J Sex Med* 2011; **8**: 1138–46.
53 Janardhan V, Bakshi R. Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. *J Neurol Sci* 2002; **205**: 51–8.
54 Marrie R, Horwitz R, Cutter G, Tyry T, Campagnolo D *et al*. The burden of mental comorbidity in multiplesclerosis: frequent, underdiagnosed, and undertreated. *Mult Scler* 2009; **15**: 385–92.
55 Alshubaili AF, Awadalla AW, Ohaeri JU, Mabrouk AA. Relationship of depression, disability, and family caregiver attitudes to the quality of life of Kuwaiti persons with multiple sclerosis: a controlled study. *BMC Neurol* 2007; **7**: 31.
56 Gregorian RS, Golden KA, Bahce A, Goodman C, Kwong WJ *et al*. Antidepressant-induced sexual dysfunction. *Ann Pharmacother* 2002; **36**: 1577–89.
57 Zemishlany Z, Weizman A. The impact of mental illness on sexual dysfunction. *Adv Psychosom Med* 2008; **29**: 89–106.
58 Hulter BM, Lundberg PO. Sexual function in women with advanced multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1995; **59**: 83–6.
59 Zorzon M, Zivadinov R, Monti Bragadin L, Moretti R, de Masi R *et al*. Sexual dysfunction in multiple sclerosis: a 2-year follow-up study. *J Neurol Sci* 2001; **187**: 1–5.
60 Laurent SM, Simons AD. Sexual dysfunction in depression and anxiety: conceptualizing sexual dysfunction as part of an internalizing dimension. *Clin Psychol Rev* 2009; **29**: 573–85.
61 Jiang J, He Y, Jiang R. Ultrastructural changes of penile cavernous tissue in multiple sclerotic rats. *J Sex Med* 2009; **6**: 2206–14.
62 Yang CC, Bowen JD, Kraft GH, Uchio EM, Kromm BG. Physiologic studies of male sexual dysfunction in multiple sclerosis. *Mult Scler* 2001; **7**: 249–54.
63 Nelson CJ, Shindel AW, Naughton CK, Ohebshalom M, Mulhall JP. Prevalence and predictors of sexual problems, relationship stress, and depression in female partners of infertile couples. *J Sex Med* 2008; **5**: 1907–14.
64 Fowler CJ, MillerJR, Sharief MK, Hussain IF, Stecher VJ *et al*. A double blind, randomised study of sildenafil citrate for erectile dysfunction in men with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2005; **76**: 700–5.
65 Lombardi G, Macchiarella A, Del Popolo G. Efficacy and safety of tadalafil for erectile dysfunction in patients with multiple sclerosis. *J Sex Med* 2010; **7**: 2192–200.
66 Safarinejad MR. Evaluation of the safety and efficacy of sildenafil citrate for erectile dysfunction in men with multiple sclerosis: a double-blind, placebo controlled, randomized study. *J Urol* 2009; **181**: 252–8.
67 Wright PJ. Comparison of phosphodiesterase type 5 (PDE5) inhibitors. *Int J Clin Pract* 2006; **60**: 967–75.
68 Giammusso B, Colpi GM, Cormio L, Ludovico G, Soli M *et al*. An open-label, randomized, flexible-dose, crossover study to assess the comparative efficacy and safety of sildenafil citrate and apomorphine hydrochloride in men with erectile dysfunction. *Urol Int* 2008; **81**: 409–15.
69 Williams G, Abbou CC, Amar ET, Desvaux P, Flam TA *et al*. Efficacy and safety of transurethral alprostadil therapy in men with erectile dysfunction. MUSE Study Group. *Br J Urol* 1998; **81**: 889–94.
70 Landtblom AM. Treatment of erectile dysfunction in multiple sclerosis. *Expert Rev Neurother* 2006; **6**: 931–5.
71 Dachille G, Ludovico GM, Pagliarulo G, Vestita G. Sexual dysfunctions in multiple sclerosis. *Minerva Urol Nefrol* 2008; **60**: 77–9.
72 Dasgupta R, Wiseman OJ, Kanabar G, Fowler CJ, Mikol DD. Efficacy of sildenafil in the treatment of female sexual dysfunction due to multiple sclerosis. *J Urol* 2004; **171**: 1189–93.
73 Schoen C, Bachmann G. Sildenafil citrate for female sexual arousal disorder: a future possibility? *Nat Rev Urol* 2009; **6**: 216–22.
74 Dhir RR, Lin HC, Canfield SE, Wang R. Combination therapy for erectile dysfunction: an update review. *Asian J Androl* 2011; **13**: 382–90.
75 Zanoli P, Benelli A, Zavatti M, Rivasi M, Baraldi C *et al*. Improved sexual behavior in male rats treated with a Chinese herbal extract: hormonal and neuronal implications. *Asian J Androl* 2008; **10**: 937–45.
76 Kim TH, Jeon SH, Hahn EJ, Paek KY, Park JK *et al*. Effects of tissue-cultured mountain ginseng (Panax ginseng CA Meyer) extract on male patients with erectile dysfunction. *Asian J Androl* 2009; **11**: 356–61.
77 Foley FW, LaRocca NG, Sanders AS, Zemon V. Rehabilitation of intimacy and sexual dysfunction in couples with multiple sclerosis. *Mult Scler* 2001; **7**: 417–21.