Multiple sclerosis and autonomic nervous system

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ABSTRACT. In the diagnosis and therapy of multiple sclerosis there is less focus on the autonomic nervous system than on the somatic nervous system. Although we have disseminated lesions of the central nervous system resulting in both somatomotor and autonomic disturbances. These involve the cerebral and spinal centers of the autonomic nervous system, as well as the pathway systems. We can see sympathetic and parasympathetic dysfunction. All autonomic functions may be disordered individually or in combined form; especially cardiovascular, urogenital and gastrointestinal functions. Autonomic disturbances should primarily be taken into account on history-taking and clinical examination at any time of the disease. Individual diagnosis and treatment is essential.
Key words: multiple sclerosis, autonomic nervous system, bladder, gut, heart.

RESUMEN. Tanto en el diagnóstico como en el tratamiento de la esclerosis múltiple existe un menor interés por el sistema nervioso autónomo que en las alteraciones del sistema nervioso somático. Sin embargo, en la esclerosis múltiple existen lesiones diseminadas que producen alteraciones en ambos sistemas. Éstas afectan a los centros autonómicos del cerebro y de la médula espinal, así como a sus vías. Por ello podemos observar tanto disfunción del sistema simpático como del parasimpático. Todas las funciones autonómicas pueden alterarse de forma individual o combinada, especialmente las funciones cardiovasculares, urogenitales y gastrointestinales. Las alteraciones autonómicas deben ser consideradas en el momento de realizar la historia y exploración clínicas, en cualquier momento de la enfermedad. Deben individualizarse tanto el diagnóstico como el tratamiento.
Palabras clave: esclerosis múltiple, sistema nervioso autónomo, vejiga, intestino, corazón.

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When attempting a simplification of the structure of the nervous system, we usually wind up with a dichotomy that delimits the somatic from the autonomic nervous system. In most diseases, the attention is unfortunately focused on the somatic nervous system with sensibility and motor function alone. This holds particularly true for multiple sclerosis, in which - in terms of diagnosis and treatment - the autonomic nervous system is near nigh being ignored in contrast to the somatic nervous system. Mostly the vegetative symptoms are described, but not analyzed and hardly ever assorted to a morphologic lesion as is done with motor and sensory disturbances. A great number of patients with autonomic dysfunctions are not treated by a neurologist but they are primarily seen by specialists of other medical fields after having been referred to them. This results in diagnostic and/or therapeutic deficits. The neurologist would either pay greater attention to autonomic disorders or cooperate more closely with other specialists. At least as far as diagnosis and treatment is concerned, autonomic disorders should be considered to be of equal importance.

❑ Anatomy

The autonomic nervous system is, simply speaking – divided into two efferent parts[1], namely the sympathetic and parasympathetic system. Again, simplifying, we can distinguish central from peripheral components. The efferences are mostly in the focus, whilst the afferences are often discarded. Lesions in MS may occur throughout the CNS, i.e. in the brain and the spinal cord, impacting on efferent and afferent components of the sympathetic and parasympathetic system. As the lesions are usually no solitary phenomenon, we are dealing with very different and complex clinical pictures at the end.

The sympathetic nervous system originates in the hypothalamus and brain stem, the preganglionic sympathetic neurons of the spinal lateral horn are located in the area C8 to L3. After interchanging into the paravertebral (sympathetic nerve trunk) and prevertebral (autonomic plexus) ganglia, the postganglionic, mostly noradrenergic neurons synaptically connect to their effector organs.

The preganglial neurons of the parasympathetic system are situated in the brain stem and in the sacral segment of the spinal cord. The cranial preganglial axons approach the cephalic ganglia via cranial nerves III, VII, IX and X and postganglially they proceed via cholinergic muscarinergic synapses to the eyes, lacrimal and salivary glands, heart, lungs and gastrointestinal tract. The sacral neurons (S2-S4) control the urogenital tract and anorectum. The enteric nervous system may be considered particularly important as it constitutes an independent part of the autonomic nervous system supplying the gastrointestinal tract from the oral down to the anal region. There is still some dispute even today as to an affer-

ent part belonging to the autonomic nervous system. The presumption prevails that there are afferences from the internal organs, skin and vessels that enter into an automatic control system with the efferences[2]. That apart, there are complex relations that have not been fully elucidated yet[3].

❑ Diagnosis of autonomic dysfunctions

All autonomic dysfunctions have in common that that diagnostic tests[4] are valid only in conjunction with medical history and clinical findings, i.e. no test by itself warrants a diagnosis, let alone treatment. Compared with the autonomic disturbances seen in other diseases, we never explicitly know where the lesion is located, whether there might be a number of lesions or whether the lesion will remain a permanent one.

The most extensive testing available pertains to cardiovascular functions. Aside from that there are valid studies referring to the urogenital and gastrointestinal tract. Additional tests are usually confined to special laboratories, and their clinical significance has not yet been sufficiently validated, especially not as far as MS is concerned.

❑ Cardiovascular disorders

Heart rate and blood pressure are the paramount parameters of cardiovascular function. It rarely happens that MS-patients spontaneously relate cardiovascular symptoms. On direct questioning though, many patients complain of poor physical performance and they tire easily, but hardly ever do they describe symptoms of orthostatic dysregulation. Cardiovascular function tests, however, frequently disclose clinically relevant disorders of the cardiovascular system. Lacking cardiovascular adaption may sometimes lead to fatigue[5].

Some work groups found orthostatic dysregulations in up to 25% of the MS patients studied[6-8]. Other authors[9, 10] do not recount any abnormalities on orthostatic tests. The same holds true for the reported clinical symptoms. All in all, we should note that orthostatic dysregulation – the cardinal symptom of many autonomic disorders – never comes as the primary symptom or subequivalent of multiple sclerosis, and even in the late stage of disease it is observed only in a small group of patients. The excellent compensation mechanisms developed by the mostly younger patients may explain that phenomenon.

Several work groups carried out standardized serial parasympathetic and sympathetic tests in selected or consecutive patients, partly with controls. The results and correlations don't fit in with a uniform picture: Merkelbach and coworkers found the grip test (in 43% of the patients studied) to be most remarkably pointing to a sympathetic dysfunction (see Table I). There is no difference between the varied courses of the disease. McDougall related a 30:15 ratio, implying that a parasympathetic test in 16% of his patients indicated the most common pathology. De Seze makes mention of blood pressure monitoring in orthostasis – a method to test sympathetic function - in 18% as the most frequent abnormality which correlates significantly to a primary or secondary chronic form of disease[6].

Table I Examinations of the autonomic nervous systems[4]

Function test	Test item	Tested system
Ewing test	Heart rate quotient (30:15 ratio)	Parasympathetic
Breath test	Heart rate difference	Parasympathetic
Valsalva's maneuver	Heart rate quotient (Valsalva's ratio)	Parasympathetic
Schellong's test	Difference in blood pressure	Sympathetic
Grip test	Difference in blood pressure	Sympathetic

Flachenecker[11] found a significant difference between active and inactive illness merely in Valsalva's maneuver – a parasympathetic test.

There are no MS-specific approaches for the treatment of these rare orthostatic problems. Basic measures include an adequate fluid intake and a high-salt diet. Elastic stockings should also be prescribed. As to medication, blood volume can be stabilized by the application of fludrocortisone and a sympathomimetic drugs (midrodrine for instance). Regarding possible disruptions of heart rate variability, there is no treatment to resort to.

❑ Disorders of the gastrointestinal tract

Central steering and complex automatic control systems are not only responsible for the parasympathically guided motility of the gastrointestinal tract as a whole but also for sphincter and continence function. This is why disordered bowel function is one of the typical sequelae of cerebral and spinal lesions of the nervous systems and, in these cases, mostly associated with sensorimotor disturbances aside from damage to autonomic fibers. This enables data on the incidence of gastrointestinal disorders in MS pa-

tients, but whether and to what extent related to the underlying disease cannot be specified, and a clear categorization to a site of lesion oftentimes remains speculative.

On direct questioning, constipation is a complaint given by 36 to 54% of the MS patients[12]. This symptomatology is generally rated lower than the symptoms of bladder dysfunction which is usually present as well. It is remarkable that nearly as many patients do report at least transitory anal incontinence[13]. Constipation and incontinence of feces is altogether more common when disordered evacuation of the bladder is a concomitant problem[14].

All of the MS patients complaining about constipation by criteria of set definition, or about anal incontinence that is not temporary, should also be seen by a gastroenterologist and proctologist. MS-induced constipation seems likely in the presence of major damage to the pyramidal tract, secondary to generalized immobility, increased tone of the pelvic floor muscles and paresis of the muscles of the abdomen. A mechanism with paradoxical contractions of the pelvic floor was described, comparable to the corresponding bladder disorder[15]. There are no definite data regarding the question as to whether an MS-specific intestinal motility disorder might be caused by impaired afferences of the intestinal mucosa or anus, and by lesions impeding the parasympathetic distribution. Lesions in the dorsal vagal nucleus could at least explain reduced motility involving the entire gastrointestinal tract to the left colonic flexure.

The diagnosis of disturbed bowel function encompasses not only the afore-said interdisciplinary clinical examinations but the determination of colonic transit time and anal manometry as well. These two examinations can help MS patients objectivate their described complaints[16]. An electromyographic examination of the external anal sphincter muscle can confirm both increased tonus and increased reflex activation[17]. A clinically simple test is the observation of food constituents in the stool, e.g. the passage time of poppy seeds or kernels of corn (3 days maximum). Digital examination is helpful in addition since the rectum shouldn‘t be filled, and clinical evidence of severe constipation is established when coproliths are felt.

There are no studies yet regarding the diagnosis and treatment of functional disorders of the upper gastrointestinal tract.

Therapeutic procedures to improve impaired intestinal motility are less focused on MS-specific measures than on general ones: Conservative management is recommended in the form of physical activity in spite of handicap, along with an ample fluid intake and dietary changes. Medication includes laxatives – macrogol for example – and even clysters in some cases. Prucalopride is expected to show some effect but specific data have not been published to date. Digital removal of fecal matter from the rectum may be called for in seriously afflicted patients. Pronounced spasticity of the anal sphincter can be reduced by injecting botulinum toxin into the sphincter. Incontinence of feces requires care by perineal pads and other aids.

❑ Dysfunctions of the urinary bladder

The most common and clinically most relevant autonomic disorders entail bladder function. This concerns urinary retention as well as voiding of the bladder. In 5 to 9% of the patients they are even the first manifestation of multiple sclerosis[18, 19]. In later stages of the illness, approx. 80% of all the patients are suffering from bladder dysfunction[12, 20]. Complete remission of intermittent bladder dysfunction is basically possible as acute symptoms subside.

The regionally disseminated activity of MS damages structures of the complex automatic control system of neurogenic bladder function at various sites: Via damage to the afferences and the pyramidal tract, spinal lesions in the cervical and thoracic cord will result in reduced central inhibition of the sacral micturition center. This, in turn, leads to uncontrolled voiding of the bladder due to hyperreflexia, to the missing coordination between detrusor activity and sphincter relaxation and largely to increased tone of the sphincters and pelvic floor muscles. Hyporeflexia is substantially rarer[21]. In some cases, disordered voiding of the bladder is caused by a focus in the pontine micturition center. Overall, there just seems to be a soft correlation between the character of bladder dysfunction and the pattern of lesion depicted on MRI. The relation - on the other hand - between the extent of bladder dysfunction and the degree of physical challenge besides pyramidal dysfunction has been corroborated by a good number of authors[21-23].

This is most likely explained by the highly complex automatic control systems that are synchronously affected at various sites (Figure 1). Detrusor /sphincter dyssynergy (uncoordinated interaction of detrusor and sphincters), is the most common feature followed by detrusor overactivity (uninhibited detrusor contractions even on only minor filling). Formation of residual urine is another clinically relevant problem in MS.

❑ Diagnosis of bladder dysfunctions

The diagnosis of bladder dysfunctions in patients with multiple sclerosis rests upon diligent history-

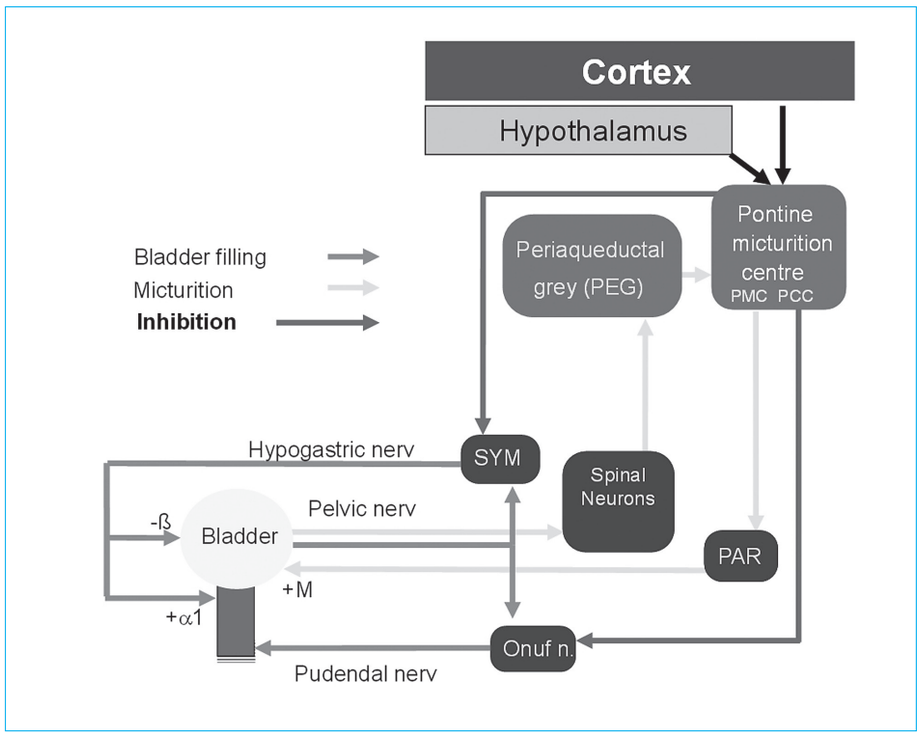

Figure 1 *Simplified model of the neurogenic loops in bladder function.*

taking. We should always explicitly ask for problems associated with passing water. Pollakisuria is frequently the first symptom the patients mention, repeatedly also in the form of newly observed nocturia. Increased voiding rates are not necessarily felt to be abnormal. Urge symptoms occurring in the later course, however, are often spontaneously related, with initially only imminent or rare incontinence. Urinary tract infections, as a rule, are not playing a decisive part at that stage of bladder dysfunction. By history already, we can distinguish between an urge- or stress-induced incontinence.

Difficult voiding of the bladder is a rare first urological symptom of multiple sclerosis. It is usually spontaneously recounted and should be investigated and treated at once. Both, acute complications and vesical alterations as secondary longterm effects can be prevented that way.

In more advanced stages of the disease, absent storage function as well as incomplete bladder evacuation are entering the clinical picture. Whereas aggravated incontinence particularly makes for social restrictions, associated bladder infections are more frequently seen now owing to the increased formation of residual urine. Contrary to traumatic paraplegic lesions, damage of the upper urinary tract is significantly less common, especially in female MS patients[24]. Deteriorating bladder function is most often accompanied by likewise slowly progressing functional disturbance of the sensory and particularly motor pathways to the lower limbs.

Video-guided urodynamic examination - recording bladder filling and voiding - permits the most accurate analysis of impaired bladder function. The data from history and urodynamic findings do not correlate[25]. Monitored are the internal pressure of the bladder, intrarectal pressure, voided volume, urinary flow and the muscular activity of the pelvic floor. The typical result in MS patients is missing relaxation and/or rising tone of the voluntary sphincters and of the pelvic floor muscles even, which hamper the voiding process. This phenomenon is called detrusor sphincter dyssynergia (DSD). The sonographic determination of residual urine can principally not identify the character of reflex disturbance; it does measure the therapeutically most significant quantity though. It is therefore suitable for therapeutic control and a gross estimate for the need of treatment. Electrophysiologic tests are to little avail. Testing the SSEP of the pudendal nerve helps in the objectivation of the degree of damage to the sensible fibers. An EMG of the voluntary sphincter can provide clues in terms of differential diagnosis.

Aside from DSD typically found in MS patients, there may principally be other bladder disorders as well. In elderly male patients a voiding disorder may be overlaid by urethral narrowing related to prostatic

Table II Commonly used drugs to treat detrusor hyperactivity

Active ingredient	Trade name	Dose/day	Principle of action
Oxybutynine	Dridase® Kentera®	2-3 x 5 mg Patch	Muscarine receptor antagonist (M1, M2, M3); spasmolytic, local anesthetic
Tolterodine*	Detrusitol®	2 x 2 mg	M2, M3 receptor antagonist
Trospium*	Spasmex®	3 x 5-15 mg	Quartary amin, no central side effects
Propiverine	Mictonetten® Mictonorm®	3-9 x 5 mg 2-3 x 15 mg	Non selective muscarinergic receptor antagonist Ca-antagonist
Emepronium*	Uro-Ripirin®	2-3 x 165 mg	Antimuscarinic and antinicotinergic
Flavoxate	Spasuret®	3-4 x 200 mg	Immediately relaxing
Darifenacin*	Emselex®	5-7,5 mg	Selective M3 receptor antagonist
Solifenacin*	Vesikur®	5-10 mg	Selective M3 receptor antagonist
Fesoterodine*	Toviaz®	4-8 mg	Selective M3 receptor-antagonist

**Purely anticholinergic agents.*

hyperplasia, and female patients frequently report additional symptoms of stress incontinence. These two differential diagnoses, however, essentially apply to middle-aged people or persons advanced in years.

❑ Treatment of disordered bladder function

The therapy of bladder dysfunction has several objectives: For once the suppression of repeated reflectory voiding of the bladder, and secondly relaxation of the sphincters to ameliorate urinary output. Continence is supposed to be maintained and renal function must not be impaired. Inhibition of bladder evacuation is afforded by the drug-induced suppression of parasympathetic activity[26, 27]. The medications commonly in use are named in Table II along with their pertinent dosage. In some cases, the local injection of botulinum toxin is the therapeutically most efficient approach[27-29]. In many countries this treatment was approved in 2011 after its efficacy had been verified by many controlled studies. Patients with mild urge incontinence will benefit from the anticholinergic action of tricyclic antidepressants.

The initiation of treatment bears the risk of developing residual urine. The sonographic determination of residual urine should thus not be neglected during that period, as is common practice anyways when someone is on other parasympatheticolytic or sympathomimetic medication. Concomitant treatment of the voiding disorder will eventually be indicated when residual volume exceeds 100 ml. Antispastic agents - frequently already used independently of bladder dysfunction - may then be administered. Bladder dysfunction of longer standing is occasionally the only indication for its application.

In spite of differentiated medication, we cannot always prevent increasing formation of residual urine in the course of treatment, or deteriorating continence. These two problems can usually be overcome by intermittent self-catheterism, which requires physical perequisites, namely adequate manual aptness and a relatively normal adductor tonus. Treatment of paraspasticity may, in some cases, help improve bladder function.

A permanent (indwelling) catheter is the "come-in second" choice for patients who don't meet these requirements or who fail in the handling of catheterism for whatever reason.

Sacral neuromodulation[30] in MS patients has proved successful merely in a few cases. Physiotherapeutic approaches can be tried along with pharmacotherapy. Muscular training of the pelvic floor and feedback techniques enhance the preservation of continence and support relaxation of the voluntary sphincter.

❑ Sexual dysfunctions

Sexual dysfunctions are so much more multifactorial in nature than disordered bladder function, and besides, they can be decisively influenced by non organic factors. Extracting that from history is a painstaking job since we are facing a diversity of symptoms, insecurities of physician and patient alike in dealing with the delicate subject. There are hardly any reliable data for comparison.

Erectile dysfunction is the most widely studied single organic symptom in men suffering from MS. Its prevalence is rated approx. 60% in the scientific literature, older studies included[31-34]. A sexologic study enrolling MS patients in northern

Germany quotes erectile dysfunction in 42% of the diseased males[35]. To validate these results it is necessary to consider the data of similar symptoms before the onset of MS, or from a control. The corresponding finding of sexual dysfunction according to DSM-IV in female MS patients has not been systematically researched, and is in particular not reflected in the older literature. The mentioned retrospective inquiry conducted by Beier revealed a prevalence of 18%[35]. Failure to have an orgasm was reported by a total 51% of the men and by 22% of the women in that study. Neurological surveys with substantially smaller groups recount 64% of the men and 58%, 12% respectively of the women with anorgasmia or a reduced capacity to experience orgasms[12, 36]. Impaired libido or disturbances of sexual appetence (by DSM-IV nomenclature) seem to be more common in MS-afflicted men. About one third of the patients claims to be affected.

The relation between individual pathway disturbances, the overall degree of disability, and bladder dysfunction with dyspareunia has been repeatedly studied. Sexual dysfunctions worsen in the course of the disease, thus presenting the typical behavior of disordered single function in MS patients. Moreover, it apparently holds true for men that their impotency is largely linked to bladder dysfunction and pyramidal tract lesion[22]. Women don't seem to encounter anorgasmia in conjunction with bladder dysfunction that extent[37]. Diminished lubrication and sensory disturbances in the genital region, however, are frequently associated with the sexual problems of female MS patients[34].

The far-reaching impact of communicating a diagnosis – unrelated to the actual degree of organically explainable dysfunctions – is illustrated by the fact that the sexual satisfaction of patients and their partners is significantly abated after hearing the diagnosis[35].

Diagnostic procedures regarding sexual dysfunctions in MS patients also differ from the comparable situation of previously healthy subjects inasmuch that detailed neurological diagnosis by exclusion can usually be refrained from. An urological and gynecological coevaluation is nonetheless advisable to single out a non-neurologic origin. Disturbed sensibility can be confirmed by SSEP of the pudendal nerve.

Erectile dysfunction is particularly responsive to treatment[26]. The introduction of phosphodiesterase-5 inhibitors has made former trials obsolete (yohimbin, apomorphine). A positive effect is reported for up to 90% of the patients[38].

Intracavernous prostaglandin injections and vacuum pumps are reserved to exceptions. Should PDE-5 inhibitors be contraindicated, MUSE (medicated urethral system for erection) might be used instead. A truly ascertained drug regimen to treat sexual dysfunctions in female MS patients does not exist. In some cases, lubrication can be improved by the topical application of estrogens.

❑ Other disorders involving the autonomic nervous system

Sympathetic skin response had been studied in different groups of MS patients. Several work groups[6, 9, 39, 40] relate pathologic results in 40 to 50% of the patients. Both, absence of response as well as delayed response were described; pathologic leg leads being more common. Conspicuous measurements amounted to 94% in some cases[41]. Simultaneous clinical symptoms in relation to autonomic dysfunction were not always reported. For some patients, there turned out to be a positive correlation to the duration of their illness, for others to the degree of MS-induced disability.

Pupillometric tests with MS patients have not yet been scrutinized enough. The basically attractive possibility to evaluate an automatic control system by sympathetic and parasympathetic impacts on pupil size is limited by the fact that many patients had suffered from optic neuritis before which resulted in considerable disruption of the physiologic control system. A uniform cardinal parameter could not be established in these measurements. The conclusions drawn from these measurements are incoherent[42].

Autonomic dysfunctions are not exclusively responsible for symptoms like fatigue, sleep disorders, thermoregulation and pain[7, 39, 43] albeit being indicative of some sort of a relationship. It will take further basic research to shed more light on that subject.

BIBLIOGRAFÍA

1.- Shields RW. Functional anatomy of the autonomic nervous system. J Clin Neurophysiol 1993;10:2-16.
2.- Bennarroch EE. The central autonomic network: Functional organization, dysfunction and perspective. Mayo Clin Proc 1993;68:988-1001.

3.- Oribe E. Testing autonomic function. In: Appenzeller O (ed). The autonomic nervous system Part I: Normal functions. Handbook of Clinical Neurology 1999;74:595-647.
4.- Jost WH, Kirchhöfer U, Bellon AK, Schimrigk K. Funktionsuntersuchungen des autonomen Nervensystems. Z Ges Inn Medizin 1993;48:469-75.
5.- Merico A, Piccione F, Levedianos G, Vescovo G, Tonin P. Autonomic and cardiac testing in multiple sclerosis patients complaining fatigue during rehabilitative treatment. Basic Appl Myol 2005;15:87-92.
6.- de Seze J, Stojkovic T, Gauvrit JY, Devos D, Ayachi M, Cassim F, Saint Michel T, Pruvo JP, Guieu JD, Vermersch P. Autonomic dysfunction in multiple sclerosis: cervical spinal cord atrophy correlates. J Neurol 2001;248:297-303.
7.- Merkelbach S, Dillmann U, Kölmel C, Holz I, Muller M. Cardiovascular autonomic dysregulation and fatigue in multiple sclerosis. Mult Scler 2001;7:320-6.
8.- Merkelbach S, Haensch CA, Hemmer B, Koehler J, König NH, Ziemssen T. Multiple sclerosis and the autonomic nervous system. J Neurol 2006;253 Suppl 1:I21-25.
9.- McDougall AJ, McLeod JG. Autonomic nervous system function in multiple sclerosis. J Neurol Sci 2003;215:79-85.
10.- Sterman AB, Coyle PK, Panasci DJ, Grimson R. Disseminated abnormalities of cardiovascular autonomic functions in multiple sclerosis. Neurology 1985;35:1665-8.
11.- Flachenecker P, Reiners K, Krauser M, Wolf A, Toyka KV. Autonomic dysfunction in multiple sclerosis is related to disease activity and progression of disability. Mult Scler 2001;7:327-34.
12.- Hennessey A, Robertson NP, Swingler R, Compston DAS. Urinary, faecal and sexual dysfunction in patients with multiple sclerosis. J Neurol 1999;246:1027-32.
13.- Hinds JP, Eidelman BH, Wald A. Prevalence of bowel dysfunction in multiple sclerosis: A population survey. Gastroenterology 1990;98:1538-42.
14.- Chia YW, Fowler CJ, Kamm MA, Henry MM, Lemieux MC, Swash M. Prevalence of bowel dysfunction in patients with multiple sclerosis and bladder dysfunction. J Neurol 1995;242:105-8.
15.- Chia YW, Gill KP, Jameson JS, Forti AD, Henry MM, Swash M, Shorvon PJ. Paradoxical puborectalis contraction is a feature of constipation in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 1996;60:31-5.
16.- Weber J, Grise P, Roquebert M, Hellot MF, Mihout B, Samson M, Beuret-Blanquart F, Pasquis P, Denis P. Radiopaque markers transit and anorectal manometry in 16 patients with multiple sclerosis and urinary bladder dysfunction. Dis Colon Rectum 1987;30:95-100.
17.- Jost WH, Schrank B, Herold A, Leiß O. Functional outlet obstruction: Anismus, spastic pelvic floor syndrome, and dyscoordination of the voluntary sphincter muscles. Scand J Gastroenterol 1999;34:449-53.
18.- Beer S, Kesselring J. Die Multiple Sklerose im Kanton Bern. Fortschr Neurol Psychiat 1988;56:390-7.
19.- Poser S, Poser W, Schlaf G, Firnhaber W, Lauer K, Wolter M, Evers P. Prognostic indicators in multiple sclerosis. Acta Neurol Scand 1986;74:387-92.
20.- Poser CM, Paty DW, Scheinberg LC, McDonald WI, Ebers GC (eds) The diagnosis of multiple sclerosis. Thieme-Stratton Inc, New York, 1984.
21.- Patti F, Ventimiglia B, Failla F, Genazzani AA, Reggio A. Micturition disorders in multiple sclerosis patients: neurological, neurourodynamic and magnetic resonance findings. Eur J Neurol 1997;4:259-65.
22.- Betts CD, D`Mellow MT, Fowler CJ. Urinary symptoms and the neurological features of bladder dysfunction in multiple sclerosis. J Neurol Neurosurg Psychiatrie 1993;56:245-50.
23.- Pozzilli C, Grasso MG, Bastianello S, Anzini A, Salvetti M, Bozzao L, Von Heland M, Fieschi C. Structural Brain Correlates of Neurourologic Abnormalities in Multiple Sclerosis. Eur Neurol 1992;32:228-30.
24.- Chancellor MB, Blaivas JG. Urological and sexual problems in multiple sclerosis. Clin Neurosc 1994;2:189-95.
25.- Martín C, Salinas J, Fernández-Durán A, Fernández-Gómez J, Jiménez N, Gangoiti L. Genitourinary changes in multiple sclerosis: the need for a urodynamic study. Rev Neurol 2000;30:643-8.
26.- Fernández O. Mechanisms and current treatments of urogenital dysfunction in multiple sclerosis. J Neurol 2002; 249:1-8.
27.- Jost W, Carl S, Haensch CA, Herzog J, Jünemann KP, Seif C, Vance WN: Leitlinie Diagnostik und Therapie von neurogenen Blasenstörungen. Thieme – Verlag Stuttgart, 2012.
28.- Kalsi V, Apostolidis A, Gonzales G, Elneil S, Dasgupta P, Fowler CJ. Early effect on the overactive bladder symptoms following botulinum neurotoxin type A injections for detrusor overactivity. Eur Urol 2008;54:181-7.
29.- Reitz A, Stohrer M, Kramer G, Del Popolo G, Chartier-Kastler E, Pannek J, Burgdorfer H, Gocking K, Madersbacher H, Schumacher S, Richter R, von Tobel J, Schurch J. European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. Eur Urol 2004;45:510-5.
30.- Hohenfellner M, Dahms SE, Matzel K, Thüroff JW. Sakrale Neuromodulation der Harnblase. Urologe 2000;39:55-63.

31.- Lilius HG, Valtonen EJ, Wikstrom J. Sexual problems in patients suffering from multiple sclerosis. Scand J Soc Med 1976;4:41-4.
32.- Miller H, Simpson CA, Yeates WK. Bladder dysfunction in multiple sclerosis. Br Med J 1965;1:1265-9.
33.- Minderhoud JM, Leemhuis JG, Kremer J, Laban E, Smits PM. Sexual disturbances arising from multiple sclerosis. Acta Neurol Scand 1984;70:299-306.
34.- Zorzon M, Zivadinov R, Bosco A, Monti Bragadin L, Moretti R, Bonfigli L, Morassi P, Iona LG, Cazzato G. Sexual dysfunction in multiple sclerosis: a case-control study. I. Frequency and comparison of groups. Multiple Sclerosis 1999;5:418-27.
35.- Beier KM, Goecker D, Babinsky S, Ahlers CJ. Sexualität und Partnerschaft bei Multipler Sklerose – Ergebnisse einer empirischen Studie bei Betroffenen und ihren Partnern. Sexualmedizin 2002;9:4-22.
36.- Mattson D, Petrie M, Srivastava DK, McDermott M. Multiple Sclerosis. Sexual dysfunction and its response to medications. Arch Neurol 1995;52:862-8.
37.- Borello-France D, Leng W, O`Leary M, Xavier M, Erickson J, Chancellor MB, Cannon TW. Bladder and sexual function among women with multiple sclerosis. Mult Scler 2004;10:455-61.
38.- Fowler C, Miller J, Sharief M. Viagra (sildenafil citrate) for the treatment of erectile dysfunction in men with multiple sclerosis. Ann Neurol 1999;46:497.
39.- Haensch CA, Jörg J. Autonomic dysfunction in multiple sclerosis. J Neurol 2006;253 (Suppl.1): I3-9.
40.- Nazhel B, Irkec C, Kocer B. The roles of blink reflex and sympathetic skin response in multiple sclerosis diagnosis. Mult Scler 2002;8:500-4.
41.- Ellie B, Louboutin JP. Sympathetic skin response is abnormal in multiple sclerosis. Muscle Nerve 1995;18:185-9.
42.- Pozzesere G, Rossi P, Valle E, Froio CP, Petrucci AFG, Morocutti C. Autonomic involvement in multiple sclerosis: a pupillometric study. Clin Auton Res 1997;7:315-9.
43.- Davis SL, Wilson TE, White AT, Frohman EM. Thermoregulation in multiple sclerosis. J Appl Physiol 2010;109:1531-7.