

Symptomatic Treatment of Multiple Sclerosis

Multiple Sclerosis Therapy Consensus Group (MSTCG) of the German Multiple Sclerosis Society¹

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Key Words

Multiple sclerosis · Symptomatic treatment · Consensus guidelines · Expert opinion · Evidence-based medicine

Abstract

Besides immunomodulation and immunosuppression, the specific treatment of symptoms is an essential component of the overall management of multiple sclerosis (MS). Symptomatic treatment is aimed at the elimination or reduction of symptoms impairing the functional abilities and quality of life of the affected patients. Moreover, with symptomatic treatment the development of a secondary physical impairment due to an existing one may be avoided. Many therapeutic techniques as well as different drugs are used for the

treatment of MS symptoms, but only a few of them have been investigated, especially in MS patients, and are approved by the national health authorities. Despite an overwhelming number of publications, only a few evidence-based studies exist and consensus reports are very rare, too. Therefore, it seemed necessary to develop a consensus statement on symptomatic treatment of MS comprising existing evidence-based literature as well as therapeutic experience of neurologists who have dealt with these problems over a long time. This consensus paper contains proposals for the treatment of the most common MS symptoms: disorders of motor function and coordination, of cranial nerve function, of autonomic, cognitive, and psychological functions as well as MS-related pain syndromes and epileptic seizures.

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Introduction

Since 1999, several evidence-based treatment recommendations on immunomodulatory and immunosuppressive treatment of multiple sclerosis (MS) have been published by the Multiple Sclerosis Treatment Consensus Group (MSTCG), representing members of the Medical Advisory Boards from MS Societies of Austria, Germany and Switzerland [1–4]. These recommendations include both evidence-based knowledge and expert opinions where sufficient data from clinical trials are not yet available. The MSTCG recommendations have recently been updated and were published after approval by the Medical Advisory Boards of the Austrian, German, and Swiss MS societies and of an additional eleven European countries [1]. This paper also comments on some other current issues regarding diagnosis and standardized follow-up of MS patients. Meanwhile, these guidelines have proven to help practicing physicians by providing standards in the treatment of MS patients, especially when unequivocal scientific evidence is lacking and expert opinion is needed.

MS is characterized by numerous symptoms and signs that result from MS-related pathology and dysfunction and are not amenable to immunotherapy. Although there is a vast amount of scientific literature dealing with symptomatic MS treatment, high-quality studies are still scarce. Therefore, the MSTCG developed and published consensus guidelines based on the available evidence from clinical studies and on expert opinion collected and critically edited by a group of MS neurologists [5]. This review includes treatment guidelines for some of the most important MS symptoms:

- Motor function and coordination, e.g. spasticity, pareses, ataxia, and tremor
- Cranial nerves, e.g. diplopia, nystagmus, dysarthria, dysphagia
- Autonomic nervous system function, e.g. bladder, bowel, and sexual dysfunction
- Psychiatric and psychological problems, e.g. depression; disturbances of cognitive function, and fatigue
- Pain and paroxysmal symptoms including epileptic seizures.

The importance of symptomatic treatment and rehabilitation for MS has recently been discussed in detail by the European Multiple Sclerosis platform [6] and the European Council for Treatment and Research in MS (ECTRIMS).

The aim of symptomatic MS therapy is to eliminate or ameliorate symptoms affecting the patients' functional

abilities impairing quality of life. Moreover, secondary impairment or disability is to be avoided, including those due to contractures or pain caused by severe spasticity, or by lumbar disc degeneration and chronic immobility or joint degeneration due to gait disturbances. Ascending infections following impaired bladder function are equally important.

Many drugs and treatment methods that are widely used in the treatment of MS symptoms are still 'off-label' in most countries. Many have never been investigated in proper clinical trials in MS patients, and were not approved by the respective national or European health authorities. In addition, several treatment modalities, e.g. some antiepileptic drugs for 'neuropathic' pain, intrathecal triamcinolone acetonide for spasticity, or 4-aminopyridine to treat fatigue or heat intolerance, are being used and evaluated in MS centers and specialized hospitals but the financial impact and legal burdens often prevent pharmaceutical companies from filing an application for licensure. Thus, in the near future, health insurance companies may no more reimburse the costs of these drugs due to their off-label status, thus cutting these patients off from such treatment.

An important prerequisite for an effective symptomatic treatment is the proper classification of symptoms presented by the MS patient. As an example, there are different types of MS-related pain which have to be treated according to the presumed pathogenic mechanisms. The same holds true for bladder dysfunction, tonic spasticity, dysphagia, and others.

Therefore, consensus guidelines for the treatment of MS symptoms are urgently needed in order to preserve these important treatment modalities which should be available at least for physicians with special experience in the treatment of MS patients. It is hoped that the national agencies and insurance companies will accept consensus statements of this kind to allow reimbursement. It seems unlikely for many treatment modalities to ever undergo a full clinical trial in MS patients providing 'gold standard' type evidence (class I evidence according to the criteria published by the American Academy of Neurology [7]): (1) many of these modalities meet little interest of the pharmaceutical industry because they are of low marketing value in MS-related indications; (2) several approaches involve combination therapies which, in the absence of approval of all single components, are not amenable to FDA- or EMEA-approved treatment trials.

Methods

We performed an extensive Medline Search covering publications on all symptoms which have been dealt with in this article combined with 'multiple sclerosis' during the period from 1980 to May 2005 and then rated the references found for the respective category of evidence classes I–III; class I denoting evidence by one or more randomized controlled studies; class II: evidence by one or more well-documented clinical studies like case-control studies or cohort studies; class III: evidence by not randomized historical controls, case reports, or expert opinion. This is followed by a classification of the different treatment options into the types of recommendation A, B, C, and U, whereby A represents the strongest and U the weakest type of recommendation [7]. We added the item 'expert opinion' denoting treatments which have so far never been and probably will never be investigated on a high evidence level, but have proven to be effective from independent experts' clinical experience.

Spasticity

Spasticity in MS is caused by axonal degeneration or malfunction that may be combined with demyelinating plaques within specific descending spinal tracts. This leads to a disturbance of inhibitory interneuronal spinal network pathways and results predominantly in weakness of physiological flexor muscles, usually with increased ('spastic') muscle tone and reduced dexterity of the muscles involved. Many types of bladder dysfunction in MS are also caused by spasticity of detrusor and sphincter muscles. For clinical purposes spasticity may be classified into a tonic (with persistently elevated muscle tone) and a phasic form (with intermittently elevated muscle tone) often associated with painful cramps. In patients with severe and long-standing spasticity contractures, disturbed micturition and bowel emptying all result in nursing restrictions and impair activities and quality of daily life. On the other hand, spasticity may to a certain degree help to ameliorate muscle weakness which reduces stability of lower limbs.

Aims of treatment include:

- Elimination or avoidance of triggers which may initiate or enhance spasticity such as urogenital infections, constipation, pain, fever or pressure sores, as well as information and training for appropriate posture, positioning and body transfer
- Amelioration of motor function
- Pain reduction
- Facilitation of nursing
- Avoidance of complications like contractures and pressure sores.

Specific Treatments

Physiotherapy

Physiotherapy is generally accepted as a basic treatment option for spasticity, even if controlled studies have only rarely been performed in patients with MS or other central nervous system disorders including stroke or spinal cord injury. To our knowledge, only one study examined the effect of physiotherapy in MS-related gait disturbances. This study reported positive results (class II evidence [8]). The most common techniques, e.g. those by Bobath, Vojta, and proprioceptive neuromuscular facilitation appear to be of roughly equal efficacy, despite their different rationale [9].

Passive treatment with an isokinetic apparatus was shown to lower spastic hypertonia in legs in patients after stroke (class II evidence [10]). Moreover, treadmill training with partial body weight support, combined with Vojta-type physiotherapy, was claimed to reduce spasticity in MS patients (class III evidence [11]). Moreover, repetitive training of isolated movements may also reduce spasticity in a paretic hand (class II evidence [12]).

There are other 'passive' treatment modalities capable of lowering elevated muscle tone like specific posturing of spastic limbs during rest in the supine position or in bed-bound patients, a slowly increasing tonic extension of spastic muscles, passive mobilization of joints using motor-driven bicycles several times a day, and use of dynamic or static splints [13]. The transient beneficial effect of cooling on elevated muscle tone was well worked out [14]. Hydrotherapy, too, has proven to reduce spasticity and the need for baclofen in patients with spinal cord injury [15].

Drug Treatment

Spasticity can be ameliorated by antispastic drugs, but its efficacy needs to be demonstrated by available scores. Unfortunately, these tests have their limits in the assessment of the overall effects [16]. The drugs should be given in divided doses according to the degree and daily fluctuations of spasticity, for example 30–45 min before getting up in the morning, frequent and regular dosage, or one dose before sleep. The most effective dosage has often to be 'titrated' carefully. Rapid discontinuation of a drug should be avoided because of possible rebound effects.

Oral drug treatment: The antispastic drugs most often used orally are baclofen and tizanidine, and both particularly reduce 'spinal spasticity'. For tizanidine (2–24 mg/day p.o., class I evidence [17, 18]) and baclo-

fen 10–120 mg/day p.o., class II evidence [19–21]), sufficient evidence is available to support their use, whereas dantrolene and tolperisone were not tested appropriately and therefore are used as second-line drugs. Patients undergoing antispastic treatment with these drugs often report reduced spasticity and spasticity-related pain or clonus, especially at night [22].

The strong antispastic effects of benzodiazepines are well substantiated, but their profound side effects including sedation and dependence limit their use in MS [16, 22]. The new drug gabapentin (300–3,600 mg/day), extensively studied in epilepsy and neuropathic pain syndromes, was shown to be effective in treating phasic spasticity (class I evidence [23, 24]). Unfortunately, a direct comparison between gabapentin and the established antispastic drugs is missing.

Tetrahydrocannabinol (THC) or a cannabis extract were considered candidates to relieve spasticity. In a recent placebo-controlled trial with THC in 630 patients, no significant reduction of spasticity could be found when using the Ashworth Scale. Nevertheless, the therapeutic effects on patients' overall mobility and on the subjective impression of pain reduction with THC and with cannabis extract suggest a potential usefulness of these drugs (class I evidence [25]). The latter observations have been confirmed in some smaller studies [26–28]. Based on the available evidence, the use of cannabinoids cannot be recommended, except in single refractory cases as second-line treatment when the treatment is performed by physicians with a high level of experience. The dose-dependent side effects are that of other THC products and the problem of drug dependence has not been formally studied.

Botulinum toxin is an important recent addition to the treatment of spasticity, and may especially be valuable in reducing focal limb spasticity (e.g. of adductor muscles). Two randomized, placebo-controlled studies using the commercial preparations Botox® (class II evidence [29]) or Dysport® (class I evidence [30]) demonstrated a significant reduction of spasticity in adductor muscles compared to placebo. But with higher Dysport doses (1,500 units) more adverse effects occurred compared to injections of 1,000 or 500 units [30].

For a discussion of the use of botulinum toxin in treating spastic bladder disorders, see section on 'Neurogenic bladder dysfunction'.

Intrathecal baclofen: The efficacy of continuous intrathecal baclofen infusion via an implantable pump has been demonstrated convincingly in patients with MS and severe spasticity of spinal and supraspinal origin (class II

evidence [31, 32]). Intrathecal baclofen results in a significant reduction of muscle tone and frequency of spasms and thereby has the potential to ameliorate quality of life. Unfortunately, the dose-dependent adverse effects including muscle weakness, headache, disturbance of consciousness and infections or dislocation of the catheter can be severe and even life-threatening. Therefore, continuous and skilled medical care in specialized centers is needed.

Intrathecal injection of corticosteroids (triamcinolone acetonide): This mode of treatment has been performed in some MS centers since the 1980s, but there is only limited evidence of its efficacy in spasticity of spinal origin. Moreover, no controlled studies have been performed so far comparing intrathecal triamcinolone acetonide with high-dose intravenous corticosteroids. There is only one recent follow-up study examining the effect of repeated intrathecal triamcinolone injections (40 mg every 3rd day, up to 6 times). This treatment resulted in a significant improvement of the EDSS and of walking distance. Serious side effects were not observed (class III evidence [33]). With respect to the invasive nature of treatment and the limited data available it can be recommended to be applied only by experienced neurologists.

Recommendations

- Search for hidden problems, which may increase spasticity (e.g. urinary tract infection, pain, fever).
- The mainstay of antispastic treatment is regular and intensive physiotherapy (expert opinion).
- If spasticity cannot be controlled sufficiently by physical therapy alone, baclofen or tizanidine should be given. Daily doses should be gradually increased and the maintenance dose adjusted according to the individual patient's course and severity of spasticity during the day (type A recommendation). Gabapentin may be effective, too (type A recommendation). Other oral antispastic drugs such as benzodiazepines and dantrolene should be used only as second-line treatment and on short term due to their common adverse effects.
- In severe spasticity of adductor muscles, treatment with botulinum toxin is helpful (type A recommendation). Continuous intrathecal baclofen infusion should be used only in cases with severe and otherwise uncontrollable spinal spasticity (type A recommendation).
- Application of oral cannabinoids and of intrathecal triamcinolone acetonide outside prospective clinical trials should be restricted to centers with special experience (expert opinion).

Fatigue

Up to 75% of MS patients suffer at some stage during their disease from abnormal physical or cognitive fatigue which usually increases during the day. This MS fatigue is different from common exhaustion or tiredness and limits their professional activities and social life, sometimes as the most important impairment in an individual. Heat often aggravates fatigue (Uhthoff phenomenon). Depression may be often masked by symptoms of fatigue, and it therefore represents an important differential diagnosis, especially in early stages of MS. Some scales have been developed to quantify fatigue, for instance the Fatigue Severity Scale (FSS [34]) and the modified Fatigue Impact Scale (MFIS [35]) which among themselves are only partially comparable [36]. The aims of treatment are the reduction of fatigue and the facilitation of normal activities in social and occupational life.

Specific Treatment

Cooling, Lowering of Body Temperature

Lowering of body temperature, physical training, rehabilitation and drug treatment have all been investigated [37]. Transient cooling of the body or of arms and legs using cold packs, cold baths or air-conditioning may improve postural stability and muscle strength of the legs (class II evidence [38]), gait (class III evidence [39]) and also fatigue (class III evidence [40]). Cooling garments may result in a better Multiple Sclerosis Functional Composite (MSFC, class II evidence [41]). It can result in a distinct reduction of fatigue and may last from 30–45 min up to several hours. Studies on the practicability of using cooling garments in an outpatient situation are not yet available.

Physical Training and Multimodal Rehabilitation

Aerobic training can improve subjective health and physical strength but does not affect fatigue scores significantly (class III evidence [42, 43], class II evidence [44]). Physical exercise programs may be continued regularly over at least some months. Ambulatory or in-hospital multimodal rehabilitation programs over about 6 weeks, including physiotherapy, occupational and milieu therapy, will reduce fatigue and ameliorate quality of life (class II evidence [45], class III evidence [46], class III evidence [47]).

Drug Treatment

Oral drug treatment includes amantadine, 4-aminopyridine, 3,4-diaminopyridine, pemoline, L-carnitine, and modafinil.

Amantadine sulfate: This drug leads to a moderate amelioration of subjective fatigue and of concentration, memory and problem-solving compared with placebo. It is generally well tolerated in daily doses of 200–400 mg/day (class I evidence [48], class II evidence [49]).

4-Aminopyridine (4-AP), 3,4-diaminopyridine (3,4-DAP): Aminopyridines have been investigated in some smaller double-blind studies. 4-AP seems to be superior to 3,4-DAP in the amelioration of temperature-related MS symptoms [50]. Therapeutic safety is limited due to a small therapeutic window, adverse effects include nausea and epileptic seizures in rare cases and more so with 4-AP. Up to now, neither 4-AP nor 3,4-DAP are licensed drugs in Europe, but may be manufactured on individual prescription by licensed pharmacists. Patient's written consent is necessary as in any other treatment with non-pharmaceutical chemicals.

This mode of treatment may be effective especially in temperature-related motor symptoms (Uhthoff's sign). In a double-blind and placebo-controlled study over 1 year, fatigue could be reduced and motor-evoked potentials were more pronounced especially with high 4-AP serum concentrations (4-AP >30 ng/ml, class I evidence [51]). Moreover, motor functions increase (class III evidence [52]) and may result in an amelioration of the EDSS (class II evidence [53]). A slow-release formulation of 4-AP proved to reduce fatigue (class II evidence [54]). Yet its possible effect on non-motor functions remains unknown.

Pemoline: This centrally acting stimulating drug has been shown to be effective to reduce fatigue in a dose of 75 mg, but to a lesser extent than amantadine. Lower doses (18.5 mg) were not different from placebo, while higher doses (>75 mg) may provoke severe adverse effects like impaired hepatic function, agitation, and sleep disturbances which may lead to drug withdrawal due to side effects [55].

L-Carnitine modulates mitochondrial metabolism of muscle fibers and is usually used to treat some metabolic muscle disorders. In MS-related fatigue, L-acetylcarnitine led to amelioration of different fatigue scales in 29% of patients compared to 21% of patients receiving amantadine (class I evidence [56]); up to now, these results have not been confirmed by other authors.

Modafinil: This α -adrenergic drug was originally developed for the treatment of narcolepsy. It may reduce

fatigue in doses from 200 to 400 mg/day (class III evidence [57, 58]). Important adverse effects include headache, dizziness, and agitation. A recent double-blind, placebo-controlled study by Stankoff et al. [59] could not detect any superiority of modafinil on various fatigue-related parameters (class I evidence).

Further treatments: A small cross-over trial with aspirin has recently shown some benefit on fatigue in MS [60]. Interestingly, some of the large earlier trials using immunomodulating agents suggest that they may also reduce fatigue, but few of these trials formally included measurements of fatigue within the list of their secondary endpoints [61–63]. Although in one other study the effect of β -interferons and glatiramer acetate (GLAT) on fatigue was measured using the Fatigue Impact Scale, 24.8% of patients receiving GLAT reported a reduced degree of fatigue (class II evidence [64]).

Hyperbaric oxygen treatment was also claimed to be effective, but this was not confirmed beyond the point of short-lived effects [65]. The application of a caffeine and histamine containing unguent (Procaril) or of weak magnetic fields [66] on MS-related fatigue have been published; unfortunately none of them has been confirmed by others up to now; the latter was clearly disproved in a recent controlled trial [67].

Recommendations

- Exclusion of other treatable causes of fatigue-like depression or hypothyroidism.
 - Cooling of the body or of extremities (type A recommendation).
 - Drug treatment with amantadine (few adverse effects, type A recommendation). If insufficient effect: 4-AP (type A recommendation), L-acetylcarnitine (type B recommendation) or modafinil (expert opinion, type U recommendation).
 - Complementary: rehabilitation with energy-efficiency training (type B recommendation).
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MS-Related Pain Syndromes

The frequency of clinically relevant pain is reported by 29 up to 86% of MS patients. These figures vary considerably due to different study design. MS-related pain may be classified into four main categories:

- *Directly MS-related pain:* Acute optic neuritis, headache due to a demyelinating lesion within the brainstem or cervical spinal cord, pseudoradicular pain;

paroxysmal syndromes (trigeminal and other neuralgias including radicular pain syndromes, paroxysmal dystonia with painful muscle spasms, Lhermitte's sign); chronic painful dys- and paresthesias, thalamic pain.

- *Pain as indirect sequel of other MS symptoms:* Joint- and muscle-related pain due to longstanding abnormal posture, spasticity, contractures, pressure sores, decubital ulcer; visceral pain; peripheral nerve lesions due to chronic pressure, e.g. poorly fitted orthoses.
- *Pain following drug treatment,* especially β -interferons.
- *MS-independent pain:* Chronic low back pain in the realm of degenerative spinal column diseases; osteoporosis, or primary headaches.

The limitation of this categorization lies in the fact that some of these pain syndromes, e.g. low back pain, may be classified into more than one group.

Only few evidence-based studies on treatment of MS-related pain syndromes have been published. Thus, most treatments used today have been investigated in neuropathic and nociceptive pain resulting from other diseases. Duration, severity, accompanying symptoms, triggers and treatments used should be documented within a pain diary. Severity of pain may be estimated using a visual analogue scale. Treatment is aimed at reducing pain resulting in lesser restriction of mobility, ability and psychosocial sequels, and thus ameliorating quality of life.

Specific Treatment

The mode of treatment depends on the type of pain the patient presents and therefore its exact differentiation is crucial. Whenever possible, physiotherapy and occupational therapy should be used since they suggest an 'active action against pain'. If development of chronic pain is impending, an additive psychological treatment within a multimodal overall plan is indicated.

Directly MS-related pain: In acute optic neuritis, intravenous corticosteroids should be applied [1], mostly reducing pain within a short time. For treatment recommendations of neuralgias and paroxysmal dystonia, see section on 'Paroxysmal Symptoms'.

Directly MS-related chronic pain often presents with unpleasant 'burning' dysesthesias of arms, legs, or trunk. They may be bilaterally and asymmetrical. This neuropathic pain is present in different neurological disorders and can be alleviated effectively by tricyclic antidepressants like amitriptyline (25–150 mg/day) or antiepileptic

agents like carbamazepine (200–1,600 mg/day, meta-analysis [68]). Similar effects can be achieved with gabapentin (300–2,400 mg/day) and lamotrigine (200–400 mg/day; meta-analysis [69], class I–II evidence [70]) or pregabalin (150–600 mg/day; class I evidence [71, 72]). Neuropathic pain in MS patients has been ameliorated by gabapentin (300–2400 mg/day; class III evidence [73]) or topiramate (200–300 mg/day; class III evidence [74]).

If opioids are used in treatment escalation for central pain, high dosages are required in most cases [75] and will therefore not be tolerated by many on long-term treatment, e.g. morphine 9–30 mg/day (class II evidence [76]).

Serotonin reuptake inhibitors (SSRIs) appear not as effective as tricyclic antidepressants [68]. Newer antidepressants [77] like mirtazapine which indirectly enhance noradrenergic and serotonergic transmission, the dual serotonin-noradrenaline reuptake inhibitors venlafaxin (class II evidence [78, 79] and duloxetine [80] as well as the noradrenaline reuptake inhibitor reboxetine (class III evidence [81]) may in the near future offer some additional treatment options.

Up to now the impact of cannabinoids cannot be assessed precisely: In one study with the primary endpoint of reduction of MS-related spasticity, a significant amelioration of pain compared to placebo has been reported [25]. Unfortunately the type of pain was not been described in detail. In another study, dronabinol proved to be more effective in the treatment of MS-related central pain than placebo [82].

Pain as indirect sequel of MS: These pain syndromes mostly result from excessive burden of joints and muscles. They may present (1) as low back pain, knee or hip pain due to pronounced limping with central gait disorders, or (2) as radicular or pseudoradicular pain of cervical and lumbar spine.

The patients should be informed on the probable causal relation between pain and abnormal gait or posture. Moreover, they should be encouraged to actively work on acquiring a near-physiologic gait. Spasticity, if present, should be treated long term by physiotherapy and drug treatment. Mechanical aids (orthoses) when needed must be custom-fitted and tested when in use.

Chronic neck pain is often present in patients with pronounced muscular weakness and in wheelchair-bound patients. In these cases, therapeutic exercises with ‘proprioceptive re-education’ is recommended for reduction of pain [83]. Manual therapy with spinal mobilization seems to be superior to conventional physiotherapy (class II evidence [84]). Shoulder pain may be alleviated

convincingly by ultrasound treatment for calcified tendinopathy [83].

Drug treatment of these pain syndromes should follow published guidelines for therapy of degenerative arthropathies since no MS-specific studies exist [85].

Pain as well as painful sensory symptoms due to pressure lesions or chronic entrapment (e.g. of peroneal nerve), of carpal tunnel or sulcus ulnaris syndrome require adjustment of mechanical aids (splints, wheelchairs, sticks) completed by physiotherapy and occupational therapy, especially if pronounced ataxia or spasticity is present. Prevention of decubital ulcers requires optimization of posture, body position, and special beds and mattresses.

Pain following drug treatment: Local pain during treatment with β -interferons or GLAT may be prevented by application of cold packs before and after injection and by optimized mode of injection as indicated in the patient brochures. Flu-like symptoms with muscular pain can be alleviated with paracetamol, acetaminophen, ibuprofen, other non-steroidal antirheumatics or low-dose corticosteroids. The effectiveness of these drugs is widely comparable (class I evidence [86], class II evidence [87]). Increasing headache during β -interferon treatment may be reduced following published guidelines of the national headache societies.

MS-independent pain: The syndrome of ‘low back pain’ is present in up to 40% of MS patients due to one or several of the following: immobilization, muscle tension, spasticity of truncal muscles, osteoporosis, chronic degenerative disc disorders and vertebral joint disease. Again, physical therapy to optimize body posture and transfer is of general help associated with well-fitted orthoses where appropriate. In some studies, chronic lumbar pain physiotherapy has proven to be effective [88] as well as acupuncture massage which was claimed to be superior to conventional massage [89]. Drug treatment should be performed according to that for chronic neck and shoulder pain [85].

Lumbar, pelvic and iliosacral pain often are pseudoradicular in origin. In radicular pain, disc herniation should be excluded. In osteoporosis, biphosphonates are the treatment of choice [90]. It should be kept in mind that repeated corticosteroid treatment at short intervals (e.g. monthly) is likely to aggravate osteoporosis.

In the complex situation of multiple pain states one should also consider surgical interventions, e.g. in profound disc protrusion or in a narrow spinal canal with possible spinal cord compression whenever this is likely to cause the pain syndrome.

Recommendations

- Specific history with patient and caretakers for pain, since these symptoms may be underreported spontaneously. Documentation in a 'pain diary', differentiation of type of pain (expert opinion).
 - For painful dysesthesias and neuropathic pain: amitriptyline or carbamazepine (type A recommendation), alternatively gabapentin, lamotrigine or pregabalin in gradually increasing doses (type A recommendation).
 - For arthralgias, neck and shoulder pain: education and treatment on the role of abnormal posturing, optimization of mechanical aids (expert opinion). Individually supervised physiotherapy (type A recommendation). Drug treatment following published guidelines (type B recommendation).
 - For flu-like symptoms and muscle pain during β -interferon therapy: acetaminophen (paracetamol) or other NSAID (type B recommendation), for local pain cold packs (expert opinion). For increasing headache drug treatment following published guidelines of the national headache societies.
 - For low back pain: physiotherapy (type A recommendation). Drug treatment following published guidelines (type B/C recommendation).
 - Newly appearing pain should be diagnosed and should not be attributed 'automatically' to MS. In most cases a longstanding and multidisciplinary treatment is necessary.
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Bladder Symptoms

Neurogenic bladder dysfunction (NBD) will occur in up to 80% of patients during the course of MS and usually impairs quality of life considerably. Sometimes, NBD is even the presenting symptom of MS and in some patients it will be the sole clinical complaint.

Detrusor hyperactivity with restricted storage capacity, urgency, increased frequency of micturition, and incontinence are the most common types of NBD. Detrusor-sphincter-dyssynergia presents with urgency, delayed bladder emptying, retention of urine, and incontinence. A hypocontractile detrusor will cause incomplete bladder emptying with elevated residual volume.

NBD may induce recurrent urinary tract infections as well as disturbed sleep due to nocturia or abdominal pain thus increasing spasticity, too. After many years, NBD will often result in detrusor hyperreflexia with an obstructive component and the risk for kidney damage.

Since the type and degree of NBD may change over time, all procedures should be based on information derived from micturition diary, serum creatinine, urea, mi-

crobiological examination, and regular measurement of residual volume. Uroflowmetry, sonography of the urinary tract and urodynamometry may help to differentiate the various pathologic mechanisms and to find proper treatment options. Cooperation with an experienced urologist is essential.

Goals of treatment are the amelioration of the bladder's storage capacity with a low-pressure storage of urine, complete voiding, reduction of micturition frequency, recovery of continence, and prevention of complications (e.g. recurrent urinary tract infections, damage of the upper urinary tract by septicemia, stone formation and reduced kidney function).

Specific Treatment

Counselling, Aids

Patients should be encouraged to keep a micturition diary, to drink adequately and regularly throughout the day (1.5–2 l/day) but not late at night, and, if a pathological residual volume is present, not to delay micturition in case of urgency. Bladder training (Cochrane Report [91]; class II evidence [92]) as well as toilet training [93] seem to be effective. Moreover, counselling on aids like insets, condom urinals or other devices to treat incontinence is useful.

Physiotherapy

Biofeedback and pelvic floor training may lead to a reduction of urgency and incontinence without normalization of urodynamic parameters during treatment [94, 95]. Combined pelvic floor training and electrical stimulation in 80 MS patients with low residual volume reduced micturition frequency, urgency and incontinence, especially in men (class III evidence [96]).

Drug Treatment

Drugs to reduce detrusor activity: Anticholinergic compounds: The positive effect of oxybutynin and tolterodine to reduce incontinence and urgency in hyperactive bladder has been proven in several studies with class I evidence (Cochrane Report [94, 97–100]). The anticholinergic side effects may be attenuated by symptomatic treatment, slow-release formulations, or a newly developed oxybutynin-containing matrix transdermal adhesive [101]. Trospium chloride (40–60 mg/day) is comparable to oxybutynin, but may cause fewer anticholinergic side effects. Propiverine (45 mg/day) has a positive effect on detrusor hyperreflexia and has also fewer anticholinergic

effects than oxybutynin. Adverse effects on the central nervous system seem to be less pronounced with trospium chloride or tolterodine than with oxybutynin (45 vs. 4 vs. 15 mg [102]). Studies on flavoxate in patients with urge incontinence are only of class II evidence [103]. The new anticholinergic agents darifenacin (meta-analysis, class I evidence [104]) and solifenacin (class I evidence [105, 106]) may reduce urgency, micturition frequency and incontinence effectively.

The α -blocking agents alfuzosine and tamsulosine aim at reducing an elevated voiding obstruction of the bladder especially in patients with simultaneous detrusor hyperreflexia. Tamsulosine (0.4 resp. 0.8 mg once daily) improves storage capacity and emptying of the bladder (class II evidence [107]). *Antispastic agents*: Baclofen has a positive effect in spastic or dyssynergic sphincter when given orally (class III evidence [108], class III evidence [109]). Because of its common systemic side effects, baclofen is only a second-line drug for treatment of overactive bladder unless low doses are effective.

Desmopressin, the antidiuretic hormone, effectively reduces nocturnal micturition frequency (class II evidence [110, 111]) and may be helpful for patients attending social activities like theatre or concert. Desmopressin should only be given to patients with normal function of the heart and the kidneys. Dose should not exceed 20 μ g intranasally [112], then treatment is mostly free of side effects [113].

Treatment of acute bladder infection: In patients with NBD, bladder infections are common and should be treated with targeted antibiotics [114] for at least 10 days. Differentiation of bacteriuria versus unequivocal infection sometimes may be difficult because of coexisting sensory disturbances or urge incontinence. Laboratory findings including leukocyturia, elevated white blood cells and erythrocyte sedimentation rate or C-reactive protein may help to make the diagnosis. Due to the short resting time of urine within the bladder, the nitrite test may be falsely negative even with nitrite secreting bacteria.

Prophylaxis of recurrent bladder infection: Low intravesical pressure and low residual volume should be achieved in order to reduce the frequency of urinary tract infection [115]. For prophylaxis of infection, methenamine (2 \times 1 g/day, class III evidence [116]) and methionine (3 \times 500 mg/day, class III evidence [117]) can be used whereas the efficacy of cranberry juice is questionable. The most important risk factor for complicated bladder infections is a transurethral or suprapubic catheter. In these patients, methenamine is not helpful be-

cause of its mechanism of action. Even in acidic urine (pH <6) it will take 30–90 min to release inhibitory concentrations of formaldehyde. Vitamin C has not shown to be effective [118]. The frequency of symptomatic bladder infections could not be reduced by chronic administration of cotrimoxazole [119].

The value of long-term antibiotic treatment is still debated [120] since this is likely to provoke selection of drug-resistant bacteria.

Invasive treatments: *Intermittent aseptic catheterization* with disposable catheters done 4–6 times/day is the treatment of choice in a hyperreflexive bladder with obstruction, but may also be effective in hypo/areflexive NBD [121]. Bacterial infection remains a risk and small skin or mucosal bleedings may occur.

In MS patients, catheterization may sometimes be difficult due to visual or sensory impairment, ataxia, or reduced cognitive function. Therefore a comprehensive training and supervision by a specialized nurse is mandatory [122]. Disposable catheters with integrated lubricants should be preferred when available.

Intermittent aseptic catheterization combined with drug-induced attenuation of the detrusor may be more effective than bladder emptying by trigger maneuvers, abdominal press or Credé maneuver with regard to long-term prognosis [123].

Intravesical treatment: In case of severe adverse effects of oral anticholinergics, these and other drugs such as vanilloids, capsaicin or resiniferatoxin may be administered directly into the bladder. Oxybutynin (class II evidence [124]) and trospium chloride (class II evidence [125]) have clearly shown to reduce involuntary detrusor contractions after intravesical instillation without causing unpleasant side effects. Intravesical instillation of anticholinergics may therefore be useful, especially in patients regularly performing intermittent self-catheterization.

The positive effect of intravesical capsaicin in patients with detrusor hyperreflexia could also be demonstrated in several studies (class II evidence [126]). Unfortunately, instillation is very painful. Resiniferatoxin is equally effective and causes much less pain (class III evidence [127]). Due to the limited existing data and major side effects, vanilloids cannot be recommended at present.

Continuous bladder catheter: Due to their high rate of side effects, e.g. chronic infections, imminent vesicoureteral reflux, stone formation, or bladder carcinoma, indwelling transurethral catheters be avoided whenever possible. Whenever a continuous flow system is necessary, a suprapubic fistula should be preferred. Use of

closed systems and optimal hygiene is mandatory. In patients with persistent detrusor hyperreflexia, anticholinergic drugs may be added regularly. Use of silicone catheters with antireflux systems, avoidance of disconnections, and acidification of urine are all recommended. The value of bladder flushing and of treatment with low-dose antibiotics is uncertain [120].

Botulinum toxin type A injected into a spastic bladder sphincter muscle is a promising new treatment option (class III evidence [128], although larger studies are still ongoing. In patients with detrusor hyperreflexia, cystoscopic injection into the bladder wall led to improved bladder capacity and continence could be ameliorated, with these effects lasting for up to 9 months (class III evidence [129]). An open multicenter study in 231 patients with neurogenic detrusor hyperactivity showed a clear amelioration of bladder capacity, reflex volume, and average micturition pressure after injection of 300 MU botulinum toxin type A (class III evidence [130]).

Neuromodulation and surgical procedures: Chronic S3 root stimulation using implantable electrodes may be promising in patients with hyperreflexive bladder who do not respond to any other treatment (class III evidence [131]). Nevertheless, this treatment should be restricted to very experienced and specialized centers. Other operations, e.g. sphincterotomies, stent implantations in patients with detrusor sphincter dyssynergia as well as autoaugmentation of the bladder are still under study and cannot generally be recommended; moreover, in MS the natural course of bladder dysfunction over longer time periods is often uncertain.

Recommendations

- Exclusion of bladder infection; treatment with appropriate antibiotics if infection is present.
 - Evaluation with micturition diary, clinical examination, sonographic evaluation of residual volume and uroflowmetry in case of obstruction, creatinine; creatinine clearance and sonography of the abdomen if necessary (type B recommendation).
 - Counselling for adequate fluid intake; information on incontinence devices, acidification of urine with methionine or cranberry extract (expert opinion).
 - In uncomplicated urgency, low disability status and with absent urological side effects pelvic floor training, toilet training in patients with at least partially maintained sphincter control are useful (type B recommendation); drugs to diminish detrusor hyperactivity include trospium chloride or tolterodine, oxybutynin, propiverine, solifenacin, darifenacin (type A recommendation); electrostimulation at S3 root level (type C recommendation).
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- If obstruction with or without urgency is present, urodynamicometry and initiation of treatment is recommended in cooperation with an urologist. In most cases: treatment with anticholinergic drugs combined with intermittent sterile catheterization may be of some value (expert opinion).
 - In detrusor hyperreflexia and pronounced adverse effects of oral anticholinergic drugs intravesical instillation of anticholinergics or injection of botulinum toxin type A (type C recommendation) is a treatment option.
 - Recurrent bladder infections: Counselling on specific causes, optimization of symptomatic treatment, methionine, in severe cases combined with methenamine (expert opinion); avoidance of chronic antibiotic treatment (expert opinion).
 - Severe nocturia: desmopressin 20 µg intranasally (type B recommendation).
 - Long-term catheterization and surgery is recommended only in treatment-resistant cases because of its irreversibility, late complications and unpredictable course of the disease (type C recommendation).
-

Neurogenic Bowel Dysfunction

Disturbances of bowel function like constipation and/or incontinence will occur in about 70% of MS patients. With respect to the frequency of constipation in healthy people, a causal connection MS is often questionable. On the other hand, negative sequels on some MS symptoms such as NBD and spasticity are well known. The diagnosis is made by the patients' descriptions and clinical examination. Other gastrointestinal diseases should be excluded. If constipation occurs, it is of great importance to differentiate between reduced bowel motility and disturbance of rectum and bowel emptying. In some cases, estimation of the colon transit time after oral administration of X-ray-positive markers may be helpful.

Goals of treatment are to normalize the frequency of bowel emptying, to achieve continence and to prevent (sub)ileus and pressure sores.

Specific Treatment

Physiotherapy, Aids, Medical Treatment

In a small open study, biofeedback seemed to be effective in less disabled patients [132]. The benefit of pelvic floor training has so far never been elucidated [133]. Fecal incontinence in women with weak pelvic floor muscles may be ameliorated partially by electrical stimulation

[134]. There are treatment trials providing sufficient data on the use of laxatives, drugs augmenting bowel motility, and botulinum toxin A [132, 135]. The established guidelines are likely to be applicable also in MS patients.

Recommendations

In case of prevailing constipation (expert opinion)

- Sufficient fluid intake (1.5–2 l/day), nutrition rich in dietary fiber.
- Physiotherapy (standing devices, motor-driven bicycles, colon massage).
- Pelvic floor training for relaxation of sphincter muscles, bio-feedback.
- In case of hardened feces lactulose or macrogol is recommended except if fecal incontinence is also present.
- Facilitation of rectal emptying by glycerin suppositories or rectal filling with fluids.
- In single cases: targeted utilization of ‘reflexive emptying’ (rectal emptying simultaneously with filled bladder, use of perianal trigger points, avoidance of crude sphincter extension).
- Avoidance of anticholinergic and antispastic drugs whenever possible.
- In case of painful sphincter spasticity or paradoxical sphincter/puborectal contractions injection of low-dose botulinum toxin type A (e.g. 50–100 MIU Dysport).
- Bowel motility augmenting drugs like metoclopramide and domperidone are of questionable efficacy.

In case of prevailing fecal incontinence (expert opinion)

- Regular bowel emptying every 3rd to 4th day.
 - Massive bowel emptying in case of pseudodiarrhea or ‘overflow incontinence’.
 - In women with insufficient pelvic floor muscles but partially maintained sphincter control use of pelvic floor training, combination with intra-anal electrical stimulation is possible.
 - Electromyography in patients with flaccid sphincter to rule out a peripheral neurogenic lesion.
 - Adequate aids, e.g. fitted intra-anal tampons especially in patients with maintained walking ability.
 - Meticulous skin care, prevention of pressure sores.
-

Sexual Dysfunction

Sexual dysfunctions do not only represent a problem of the individual patient but may also lead to conflicts within the partnership. Female patients often complain

of reduced libido and lack of orgasm due to diminished genital sensitivity or dyspareunia. Males predominantly suffer from erectile dysfunction (ED) and, less frequently, early or failing ejaculation. Moreover, spasticity and muscular weakness will complicate sexual intercourse in both genders.

Primary sexual dysfunctions are directly caused by MS-related demyelination whereas secondary sexual dysfunctions are the consequences of specific MS symptoms like spasticity, fatigue, or bladder dysfunction. Tertiary sexual dysfunctions comprise the manifold psychological reactions due to MS-related disabilities. Nevertheless, not every relapse or worsening of MS will affect sexual life of the patient and her/his partner [136].

During the course of MS, sexual dysfunction will eventually occur in up to 80% of patients but is probably rare within the early years of the disease. Men are affected more frequently than women (75 vs. 50%). Sexual dysfunction is usually combined with bladder dysfunction.

As patients often do not directly complain about sexual dysfunction, they should be asked for during the consultation. The goal of treatment is to normalize sexual activities of the MS patient and her/his partner as far as possible.

Specific Treatment

Before treatment a complete neurologic and sexuality-related history, neurologic examination and, in some cases, neurophysiologic studies, e.g. pudendus-SSEP, are necessary. Patients should be asked for drugs which may interfere with sexual function, e.g. antidepressants, benzodiazepines, neuroleptics, antiepileptic drugs, clonidine, or β -blockers. MS symptoms which may impair sexual intercourse like adductor spasticity or bladder infection or incontinence should be treated appropriately. Conflicts within the partnership prompt counselling by an experienced specialist and may profit from psychotherapy [137].

Drug Treatment

The phosphodiesterase-5 inhibitor sildenafil is now the most intensively studied drug for ED. 25–100 mg of sildenafil should be taken orally 1 h before sexual intercourse and will result in a significant improvement in terms of achieving as well as maintaining erections. Adverse side effects like headaches, flushing, rhinitis, dizziness, or dyspepsia were all rare and did not lead to discontinuation of treatment (class I evidence [138]).

Contraindications like coronary heart disease, recent myocardial infarcts and stroke as well as co-medication with nitrates and molsidomine have to be carefully excluded since they may be life-threatening if sildenafil is used simultaneously. In the future, the newer phosphodiesterase-5 inhibitors vardenafil and tadalafil may offer some advantages with respect of duration of effect and adverse events.

Especially in patients with cardiac dysfunction in which sildenafil and analogues are contraindicated, sublingual apomorphine may be an alternative. This drug can be used 'on demand' since its effect will start about 20 min after ingestion. Up to 6 mg will lead to a significant better erection compared to placebo (class II evidence [139]). Apomorphine may be less effective compared to sildenafil and its adverse effects, especially nausea and fatigue, will often limit its use. In patients suffering from psychogenic ED, yohimbine may ameliorate erection [140].

In female patients with reduced lubrication and resulting dyspareunia, treatment with tibolone, estrogen-containing unguents, or commercially available lubricant creams can be recommended (class III evidence [141, 142]). After treatment with sildenafil a positive effect on lubrication could be demonstrated in only a few female MS patients (class I evidence [143]).

Invasive and Surgical Treatments, Aids

After the introduction of sildenafil and analogues, invasive procedures can often be avoided. No formal comparative studies are available. Injection of prostaglandins into the cavernous body of the penis has proven to be an effective treatment (alprostadil 2.5–20 µg into the cavernous body [144]; class II evidence [145]). Transurethral application is also possible (class I evidence [146]). Patients have to be carefully instructed of some adverse effects like penile pain, dizziness as well as a long-lasting and sometimes painful erection. Treatment should be started using low doses of alprostadil. Nevertheless, after the introduction of phosphodiesterase-5 inhibitors, alprostadil is only a second-line drug for treatment of ED.

If patients tend to avoid drug treatment for ED, vacuum pumps may be considered (class III evidence [147]). Penis prostheses offer a further treatment option [148].

Recommendations

- Discontinuation of drugs which can provoke or enhance ED; treatment of bladder infections and focal spasticity (expert opinion).
 - Diagnosis and treatment of existing conflicts of partnership (expert opinion).
 - In ED treatment with sildenafil (type A recommendation). If contraindications or intolerance against sildenafil are present, treatment with sublingual apomorphine may be initiated (type B recommendation); intracavernous or transurethral alprostadil if appropriate (type B recommendations).
 - Hormone preparations like tibolone in female patients with loss of libido or dyspareunia (type B recommendation).
-

Ataxia and Tremor

During the course of their disease, about 80% of MS patients suffer from disabling ataxia which often comprises cerebellar, spinal or sensory ataxic symptoms. Truncal as well as limb ataxia of upper extremities with distal intention tremor represent one of the most disabling MS symptoms especially when combined with postural tremor and dysmetria. The degree of ataxic symptoms is often fluctuating depending on the current physical strength or psychological situation of the patients.

Quantification of ataxia may be mostly achieved using clinical and activity-of-daily-living (ADL) scores [149, 150]. The goal of treatment is amelioration of ataxia, especially when severely interfering with daily activities as well as social or occupational life.

Specific Treatment

The cornerstones of treatment are physiotherapy and occupational therapy. Drug treatment which can only reduce the tremor component, is usually less helpful. Surgical procedures only play a limited role.

Physiotherapy, Occupational Therapy

They should be embedded within an overall concept implying tonus regulation, reduction of muscular fixations, stabilization of the trunk, training of sensory skills, coordination of movements, ataxia-inhibiting techniques as well as supply with aids. Treatment using large supporting surfaces should slowly be reduced. Training should prefer methods with special respect to daily life

requirements. Moreover, appropriate aids should be used, e.g. cutlery with thickened grips and enlarged supporting areas. In patients with arm pareses or truncal instability, proprioceptive facilitation techniques may be used for the amelioration of muscle tone.

The use of wrist hefts in patients with postural tremor was shown to be ineffective [151] and, moreover, may even cause enhancement and fixation of elevated muscular tone. Whenever possible, patients should be trained to reduce muscular fixations using specific relaxation techniques.

A significant reduction of intention tremor may be achieved by short-term (1 min) local application of ice (class III evidence [149]). In another comparative study using cooling cuffs (skin temperature 18 vs. 25°C) a temperature-correlated effect on postural tremor could be demonstrated (class III evidence [152]). Local cooling may be used by the patients themselves whenever necessary, e.g. before meals, intermittent self-catheterization, or PC work.

Drug Treatment

In individual cases, antiepileptic and other centrally acting drugs as well as β -blockers can be used additionally in patients with severe intention tremor.

A clear benefit of β -blockers could only be demonstrated in essential tremor whereas propranolol was not effective in patients with cerebellar tremor (class III evidence [153]). Besides this, some patients apparently may profit from treatment with β -blockers since these drugs will mitigate psychic agitation and thus reduce tremor.

Antiepileptics. Primidone may be effective in essential tremor but sedative side effects limit its use. Gabapentin will ameliorate essential and orthostatic tremor and carbamazepine (class III evidence [154]) as well as topiramate (class III evidence [155]) may positively influence cerebellar tremor.

Other Drugs. Clonazepam (3–6 mg/day) may be of some benefit in cerebellar tremor, too [156]. The effect of oxitriptan (5-hydroxytryptophan) on ataxia of the trunk and legs usually occurs only after treatment with 3×300 mg/day over about 6 weeks (class III evidence [157]). Up to now, ondansetron, a 5-hydroxytryptophan-(HT-3) antagonist, showed conflicting results. Using 8 mg of oral ondansetron, no significant reduction of cerebellar symptoms could be demonstrated (class III evidence [158]; class III evidence [159]), whereas intravenous ondansetron (8 mg/day) caused a clear short-lasting amelioration of writing ataxia and of the patients' subjective impression (class III evidence [160]).

Isoniazid has been used in patients with cerebellar tremor with conflicting results (class III evidence [153, 161]). Adverse effects may limit treatment. Physostigmine has no significant effect on cerebellar tremor [162, 163].

Cannabinoids as well as alcohol may reduce ataxic symptoms [153, 164]. Nevertheless, treatment with these substances cannot be recommended due to insufficient data and adverse effects, especially the risk of addiction.

Surgical Treatment

With stereotactic operations, e.g. VIM thalamotomy and VIM (deep brain) stimulation, reduction of tremor could be demonstrated though VIM thalamotomy is not as effective in MS patients as in those with Parkinson's disease. Chronic VIM stimulation will produce better results but stimulation parameters probably have to be optimized repeatedly. In some smaller studies and case series, amelioration of tremor could be achieved in 87.7% and of activities of daily life in 76% of operated patients [165]. Simultaneously the level of disability and SF-36 subscales remained largely unchanged (class III evidence [166, 167]). Fortunately, peri- and postoperative complications are rare. Best treatment results may be achieved in patients with stable tremor, e.g. marked axial and proximal arm tremor, and trunk ataxia [168]. If stereotactic treatment is considered, the patients' disease course should be stabilized by effective immunotherapy for at least 1 year (expert opinion).

Recommendations

- Regular physiotherapy and occupational therapy, cooling (expert opinion).
 - In patients with predominant tremor: additional drug treatment (monotherapy) with a β -blocker (rapid assessment of efficacy) and, if not successful, monotherapy with carbamazepine, primidone or clonazepam. If escalation is necessary, combination therapy with a β -blocker and an antiepileptic drug (type U recommendation). Efficacy of these drugs is often limited by their extensive adverse effects.
 - If tremor is unresponsive to combination therapy: oxitriptan (type U recommendation).
 - Only in patients with considerable tremor unresponsive to drug treatment or with severe side effects electrical stimulation of the thalamus should be considered (type C recommendation).
-

Cognitive Dysfunction

Dysfunctions of cognitive skills of some degree may affect up to 70% of patients with long-standing MS. Impairments mostly include attentional domains, memory, executive functions, in particular 'multitasking' skills, and constructive visual skills, whereas implicit function and speech are rarely disturbed. The patients' perception of his/her cognitive dysfunction is often inadequate or even missing [169].

Diagnostic procedures should include a detailed history of the patients' capabilities in daily living and in his/her occupation followed by standardized testing of the different cognitive functions.

Specific Treatment

The treatment is aimed at the training of preserved functions and at strategies to compensate existing deficits. It is necessary to focus training on specifically disturbed cognitive functions. In many patients, several cognitive categories and affective disturbances have to be treated simultaneously.

Attention Training

Nowadays, PC-based techniques are used to treat permanent and selective alertness or activation of alertness (class III evidence [170–172]). Even the ability to cope with distracting stimuli may be ameliorated. Repeated treatment will result in better performance.

Memory Training

Pure repetitive learning is hardly effective. In less severely affected patients, training of memory strategies may be helpful, whereas severely affected patients usually need memory aids like notebooks and reminders, e.g. 'NeuroPage' (class II evidence [173], class III evidence [174], class III evidence [175]). Training and performance control should be done several times a week. Structured memory training in MS patients with moderate to severe learning impairments may lead to improved memory performance (class I evidence [176]). Simple tasks such as crossword riddles, puzzles or other games training memory skills may turn out to be of some benefit, too.

Combination of memory training with relaxation techniques, treatment of simultaneous depression, counselling and compensational strategies is helpful. Moreover, family members, other relatives or near friends may be included into the treatment process which again has

to be of adequate duration and regularity (class I evidence [177–179]).

Drug Treatment

So far, cholinesterase inhibitors like physostigmine and donepezil and, in addition, 4-AP and amantadine have been studied with respect to their effect on cognitive dysfunction. Moreover, there are some data suggesting a reduction of cognitive decline during immunomodulatory treatment of MS with β -interferons and GLAT.

Donepezil, which is used for the treatment of Alzheimer-type dementia, may ameliorate memory functions, especially verbal learning and memory, but also of alertness and executive functions (class I evidence, 10 mg/day [180], class III evidence [181]).

In severely disabled MS patients, the amplitudes of cognitive evoked potentials could be improved with amantadine but reaction time measurements did not [182]; the clinical significance of these findings has to be determined [183].

β -Interferons, GLAT: During treatment with β -interferon-1b the visuospatial performance in treated patients was stable compared to deterioration of this task in patients on placebo (class II evidence [184]). Similar results have been achieved during β -interferon-1b treatment with respect to alertness, concentration, visual learning and recognition (class II evidence [185]). On the contrary, another study using the same interferon in patients with relapsing-remitting MS failed to show any improvement of verbal memory (class III evidence [186]).

In a post-hoc evaluation of a study using β -interferon-1a, significant differences with respect to information processing, memory, visuospatial and executive functions could be demonstrated after 2 years of treatment compared to placebo (class II evidence [187]).

Studies using GLAT [188] or methotrexate [189] could not detect any improvement or even stabilization of cognitive dysfunction.

Recommendations

- Training should be aimed specifically at the disturbed cognitive function(s). High-frequency treatment is mandatory (type B recommendation).
 - Complex neuropsychological treatment is preferable, e.g. treatment of simultaneous depression, relaxation techniques, counselling within multimodal rehabilitation (type B recommendation).
 - With immunomodulatory treatment cognitive decline may be delayed.
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Table 1. Paroxysmal symptoms in multiple sclerosis

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- Trigeminal, glossopharyngeal and other neuralgias (including MS-associated (pseudo)radicular pain)
 - Sensory symptoms: paresthesias, dysesthesias, pruritus, Lhermitte's sign
 - Paroxysmal ataxia and dysarthria
 - Dyskinesias: paroxysmal dystonia (formerly: tonic brainstem seizures), facial hemispasm, tremor, akinesia (loss of muscle tone, kinesiogenic choreoathetosis)
 - Facial myokymia
 - Myoclonus, e.g. palatomyoclonus, singultus (hiccup)
 - Vertigo, nausea/vomiting, cough
 - Blurred vision, oscillopsia, convergence spasm, spasm of m. rectus superior/levator palpebrae, ocular flutter, ocular tilt
 - Uhthoff's phenomenon
-

Depression

Depressive syndromes occur in about 50% of MS patients [190] though episodic fluctuations of depressive mood (International Classification of Disease-10, ICD-10: F32, F33) or difficult coping have to be distinguished from long-term depressive states (ICD-10: F34) and 'organic' major depression (ICD-10: F06.32). Even bipolar affective psychoses in MS patients can be seen twice as much as in normal population [191]. Diagnosis will be made according to ICD-10 criteria mentioned above. Goals of treatment are the reduction of depressive mood by proper guidance and drug treatment when needed as well as prevention of suicide.

Specific Treatment

Counselling

As depression is often masked by physical symptoms (fatigue, exhaustion, cognitive problems) it should actively be searched for during the consultation. Whenever depression is obvious, a psychiatric examination should precede counselling through the local MS society chapters or by friends and family (class II evidence [192]).

Psychotherapy

Several studies demonstrate the efficacy of psychotherapy for depression in MS patients (class II evidence [179, 193, 194], class III evidence [195]). Mainly cognitive behavioral therapy has been applied, though no preference of a specific psychotherapeutic technique has been worked out.

Drug Treatment

A Cochrane review emphasizes the efficacy of tricyclic antidepressants as well as of SSRIs in depressive patients with other medical illness [196]. Treatment with desipramine combined with psychotherapy (class II evidence [191]), with sertraline and psychotherapy (class II evidence [194]), and with the monoaminooxidase (MAO) A inhibitor moclobemide (class III evidence [197]) are effective. In the individual patient the potential adverse effects may help to select the drug for treatment.

Recommendations

- Counselling as prophylactic and complementary treatment (type B recommendation).
 - Drug treatment with tricyclic antidepressants, serotonin reuptake inhibitors, noradrenalin reuptake inhibitors, MAO A inhibitors (type A recommendation).
 - Structured psychotherapy using accepted techniques, e.g. cognitive behavioral therapy (type A recommendation).
-

Paroxysmal Symptoms

About 10–20% of MS patients suffer from paroxysmal symptoms like trigeminal neuralgia (TN) and several other paroxysmal painful, sensory and – more rarely – motor symptoms (table 1). These are very short stereotypical symptoms lasting from seconds to several minutes occurring spontaneously or triggered by sensory stimulants, movement, change of body position or hyperventilation. They may appear up to several hundred times a day.

The diagnosis is made on clinical findings and should be completed by the documentation of frequency, localization, quality and intensity, duration, triggers and accompanying symptoms, e.g. using a diary.

Specific Treatment

Patients should be instructed to avoid triggers like specific movements, heat or sensory stimuli. Physiotherapy is not effective. Drug treatment mainly consists of anti-epileptic drugs, especially carbamazepine, and more recently, gabapentin. If paroxysmal symptoms occur during a relapse of MS, high-dose steroid therapy should be introduced according to established guidelines [1]. With the exception of TN treatment, high-quality studies are lacking.

Trigeminal Neuralgia

Drug Treatment

MS-associated TN is treated as any other type of TN. According to several controlled studies, carbamazepine is still the first-line drug [198]. Nevertheless, even in sufficient dosage carbamazepine may cause a paradoxical increase of some MS symptoms in single patients [199, 200]). Phenytoin, baclofen (class III evidence [201]), lamotrigine (up to 400 mg/day, class II evidence [202]), gabapentin (up to 1,600 mg, class III evidence [203, 204]), topiramate (up to 300 mg/day, class III evidence [205]), oxcarbazepine and valproate are second-line drugs. Up to now no comparative drug trials have been published.

Especially in emergency situations the efficacy of phenytoin has been proven since the drug can be injected intravenously. The efficacy of lamotrigine could be demonstrated even when combined with carbamazepine [206]. Unfortunately, the dose of lamotrigine has to be increased very slowly precluding its rapid action. The prostaglandin E₁ analogue misoprostol may offer another treatment option for TN in MS patients (600 µg/day, class III evidence [207]).

Surgical Treatment

Surgical interventions, like thermocoagulation and glycerol instillation into the cavum Meckeli are widely accepted as second-line therapies for TN [208]. Microvascular decompression of the trigeminal nerve has been performed successfully even in single MS patients (class III evidence [209]), but in some of them complete pain relief could only be achieved after partial rhizotomy. On the contrary, radiosurgery is a minimal invasive procedure and causes hypo- and dysesthesias in only 10% of patients. 75% of patients will remain free of pain even after 3 years. Unfortunately there are no data on long-term success compared to other surgical techniques (class III evidence [210]). Moreover, high-quality studies examining the efficacy of these surgical techniques in MS patients are still lacking. In MS patients with TN, the achievement of complete pain relief may require a higher number of surgical interventions to result in permanent relief when compared to TN of other origin [211].

Other Paroxysmal Symptoms

Paroxysmal paresthesias and pain may occur spontaneously or are triggered by movement or posture within one part of an extremity. They will usually last up to several minutes.

Carbamazepine is still the most important and most effective drug for the treatment of these paroxysmal symptoms and daily doses of 100–300 mg may lead to complete relief of the symptoms treated. Gabapentin (up to 1,200 mg/day, class III evidence [212]), lamotrigine (up to 400 mg/day, class III evidence [213]), phenytoin or valproate have as well been used successfully. Even with clonazepam and the sodium channel blocking agents lidocaine and mexiletine, several motor and sensory paroxysmal symptoms could be sufficiently reduced [214, 215].

Patients with Uhthoff's phenomenon should be told to avoid heat and to use cooling techniques. Moreover, 4-AP may be of some value [53]. The treatment of choice in the rare facial hemispasm is the application of botulinum toxin A once the hemispasm becomes disabling [216].

Recommendations

- In most cases, paroxysmal symptoms respond to treatment with carbamazepine (type A recommendation). If paroxysmal symptoms newly occur with an acute relapse, a high-dose steroid treatment according to established guidelines should be introduced (expert opinion).
- If carbamazepine is not sufficient or causes worsening of other MS symptoms: treatment with another antiepileptic agent like lamotrigine, gabapentin (or oxcarbazepine in patients with TN), or phenytoin, topiramate or valproate when appropriate can be tried (type U recommendation).
- For treatment of paroxysmal motor symptoms (spasm or myoclonus) treatment with clonazepam (type U recommendation).
- In patients with drug-resistant TN: consider thermocoagulation or instillation of glycerol into the cavum Meckeli, alternatively microvascular decompression or radiosurgery may be recommended (type C recommendation).

Oculomotor Symptoms

During the course of the disease about 30–50% of MS patients will suffer from oculomotor symptoms and in about 13% they may be part of the first relapse. The most important symptoms are internuclear ophthalmoplegia and different forms of nystagmus like upbeat/downbeat

nystagmus or, less commonly, pendular nystagmus. It enhances during fixation and results in oscillopsia and blurred vision.

Specific Treatment

Oculomotor symptoms occurring during a relapse should be treated with high-dose intravenous methylprednisolone. An eye patch may be helpful during the acute phase to avoid double vision.

For drug treatment of pendular nystagmus gabapentin (900–1,200 mg/day, class II evidence [217], class III evidence [218]) or memantine (40–60 mg/day, class III evidence [219]) should be used. Scopolamine adhesives, vigabatrin or baclofen are not effective.

Baclofen (3 × 5 mg/day) may reduce upbeat/downbeat nystagmus [220]. A single dose of 3,4-DAP (20 mg) will ameliorate downbeat nystagmus of different etiologies (class I evidence [221]). There are no data concerning 3,4-DAP treatment in MS patients with downbeat nystagmus. 4-AP has been successfully used so far in 2 patients (class III evidence [222, 223]).

Patients suffering from internuclear ophthalmoplegia rarely complain of blurred vision despite impressive motility defects, so that treatment is not necessary.

Recommendations

- Treatment with gabapentin or memantine in pendular nystagmus (type B recommendation).
 - For upbeat/downbeat nystagmus baclofen is the drug of first choice (type A recommendation), for downbeat nystagmus 3,4-DAP may be used (type B recommendation).
 - In internuclear ophthalmoplegia drug treatment is rarely needed.
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Dysarthria and Dysphonia

Dysarthria, a dysfunction of articulation, and dysphonia, a dysfunction of phonation, are each a component of dysarthrophonia indicating a profound incoordination of tongue, glottis, larynx and respiratory muscle movements. Estimates of its frequency range between 20 and 62%, depending on the definition of abnormality. Among their many different forms [224, 225], spastic and ataxic dysarthria are most often present in MS patients. Dysarthrophonia can be augmented by early fatigue resulting

in progressive dysfunction over a longer conversation or during a speech.

Degree of dysarthria correlates with the severity of neurological impairment and the duration of disease [225]. Important features are a dysfunction of loudness control (77%), harsh voice quality (72%), imprecise articulation (46%), impaired emphasis (39%), impaired pitch control (37%), decreased vital capacity (35%) as well as hypernasality (24%) [226]. Dysarthria and dysphonia both impair communicative and psychosocial abilities by restricting the patients' participation in professional and social life.

Severity of dysarthria may be measured by several scales, e.g. the NTID National Technical Institute for the Deaf (NTID) – scale of understandability [227], the Frenchay Dysarthria Examination [228], the Voice Handicap Index (VHI [229]) or the Voice-Related Quality of Life Index (V-RQOL [230]). Goals of treatment are the restoration of lost speech functions and thus of the ability of unimpaired communication.

Specific Treatment

Speech therapy is indicated whenever dysarthria or dysphonia interfere with correct transmittal of verbal messages; when speech and voice are not longer sufficient to facilitate everyday communication; when impaired speech, voice and communication reduce quality of life through social isolation and imminent loss of occupation, and when the patient and his relatives are increasingly stressed by dysarthria and dysphonia.

Treatment should be performed by a team comprising a neurologist, an otorhinolaryngologist and a speech therapist. Three general areas of dysfunction may underlie dysarthria/dysphonia: decreased respiratory output, decreased respiratory/phonatory coordination and control, and reduced phonatory function [231]. Techniques to modify speech behavior, drug treatment and communication aids are all important components of therapy. Unfortunately, not every MS patient is suited for treatment since rapid disease progression, cognitive and behavioral impairment and, over and above, reduced motivation will affect its success.

Behavioral Techniques

Behavioral techniques include speech tasks (phonetic, linguistic, and pragmatic methods as well as non-speech tasks (postural adjustment, breathing strategies, feedback methods and neurophysiological concepts, e.g. Bo-

bath technique, proprioceptive neuromuscular facilitation). Recently, an algorithm on existing treatment options has been developed under the auspices of the Academy of Neurologic Communication Disorders and Sciences (ANCDS) [225, 231]. Treatment consists of:

- Training of tactile and auditive perception on speech-related muscular motions.
- Aware control of usually automated processes.
- Inhibition of abnormal posture and movement.
- Measures to normalize muscle tone, e.g. enhancement of flaccid muscle tone or its reduction in spastic elevation of tone.
- Repetitive training of physiologic movements.
- Biofeedback.

In spastic and ataxic dysarthria as the most common speech disorders, control of speech rate, voice emphasis and phrase shift, reduction of phrase length and increase of voice power are the mainstays of treatment [232, 233]. Controlled studies are still lacking for MS. In patients suffering from Parkinson's disease, a beneficial effect of this treatment on loudness and dysarthria could be demonstrated but no superiority of a special technique [234–236]. In most of the Parkinson patients with hypokinetic dysarthria the 'Lee Silverman Voice Treatment' (LSVT) had been used which also may be effective in MS patients [237]. In an evidence-based evaluation it could be demonstrated that biofeedback can be effective in changing physiologic variables. However, the relationship between these changes and speech production or communicative participation has yet to be clearly established [225].

Prosthetic and Other Technical Aids

In patients with nasal speech due to impaired function of the soft palatine the velum can be elevated by a velum prosthesis fixated to the teeth to ameliorate hypernasality [238].

Technical aids like a pacing board, graduated sticks or a metronome can help to control speech velocity whereas a delayed auditory feedback unit may reduce it. 'White' (background) noise presented via headphones often leads to a spontaneous increase of loudness (Lombard effect). Alternatively, electronical voice amplifiers may be used. As with any speech behavioral technique, the effectiveness of these devices cannot be estimated sufficiently due to the small number of patients published. Nevertheless, in an ANCDS review it was stated that these devices 'may improve speech loudness and, in most cases, intelligibility of speech in individuals with hypokinetic dysarthria' [225].

Drug Treatment

There is no recommendation for the use of drugs in dysarthria. In patients with adductor spasmodic dysphonia, injections of botulinum toxin A may result in substantial improvement in several patients whereas the improvement of abductor spasmodic dysphonia seems to be less clear [239]. Additional training may enhance the positive effect of botulinum toxin A treatment [239, 240]. In MS patients there is very limited experience [241].

Surgical Treatment

For constriction of the glottis in patients with vocal chord paresis, injections of teflon or collagen fluids were reported. Phonosurgical operations may ameliorate position and tone of the vocal folds [242] and velopharyngeal surgery can be considered if a velum prosthesis is not effective [243]. None of these procedures has been formally tested in MS patients.

Speaker Strategies, Augmentative and Alternative Communication Techniques

When verbal communication is reduced to less than 50% of intelligibility, special strategies and aids should be used. Speech supplementation strategies provide additional information to the speech signal. They include alphabet supplementation in which the speaker indicates the first letter of the word spoken on an alphabet board, topic supplementation and gesture accompanying speech. It is suggested that listener training should be included into the therapeutic setting [244]. A variety of electronic communication devices have been developed including electronic typewriters and minicomputers with synthetic speech processing that supplement or replace impaired verbal communication. Communication aids may be character- or symbol-oriented. Using laser or infrared controls for transmission, these aids may be utilized even by patients suffering from severe motor impairment [233, 245].

Before these more demanding aids are introduced to MS patients, their cognitive, motor, visual and acoustic skills should first be checked and the acceptance of the patients and his interlocutor be considered [244]. A longer learning period is to be expected in an advanced MS patient than in an otherwise healthy language skills disorder.

Treatment recommendations are based only on limited clinical experience from small studies concerning therapy of dysarthria in other diseases, and on expert opinion and plausibility of methods investigated [246].

Recommendations

- Speech therapy in patients with relevant dysarthria (expert opinion).
 - Co-treatment of associated symptoms, e.g. fatigue, spasticity, tremor (expert opinion).
 - Speech supplementation techniques und communication aids in patients with severely impaired understandability despite speech therapy (expert opinion).
-

Dysphagia

Estimates on the frequency of dysphagia vary between 24 and 55% depending on the intensity of diagnostic procedures and disease progression. Severely impaired patients (EDSS 8–9) may be affected even more frequently. Occasionally, patients with an EDSS up to 2.5 may present with dysphagia but less commonly they complain about discomfort.

Difficulties in swallowing will provoke recurrent cough and increased sialorrhea. Moreover, quality of life is often markedly reduced due to impaired pleasure of drinking and eating. In severely afflicted patients, dehydration, malnutrition, and (silent) aspiration of food and/or fluids with subsequent aspiration pneumonia may cause even life-threatening problems.

Patients with impaired swallowing should undergo a careful assessment including a detailed history related to specific symptoms of dysphagia, a neurological and otorhinolaryngological examination and a functional swallowing test. When in doubt, a videofluorographic swallowing study (VFSS) and/or transnasal fiberoptic endoscopic examination of swallowing (FEES) may help in establishing a diagnosis.

The severity of dysphagia can be estimated according to clinical and radiological findings. In the near future the newly developed SWAL-QOL and SWAL-CARE outcome tools may be used additionally, which consider patients' perspectives and quality of life. They have also been validated in MS patients [247]. Goals of treatment are the avoidance of insufficient fluid and food intake, avoidance of aspiration and secondary pneumonia as well as amelioration of quality of life.

Specific Treatment

Exsiccosis, malnutrition and proven aspiration (by observing recurrent aspiration pneumonia) are urgent

indications for active treatment of dysphagia. Treatment consists of functional therapy including swallowing therapy, drug treatment and other palliative measures. A qualified speech-language pathologist is of special importance. There are no data from controlled clinical studies in MS patients with dysphagia. The evidence of a treatment effect is derived from few controlled studies in other neurologic diseases, from clinical experience, expert opinion and plausibility of treatment methods.

Functional Treatment (Swallowing Therapy)

Functional treatment comprises

- restorative (facilitation or inhibition of muscular function),
- compensatory (postural changes and swallowing techniques/maneuvers) and
- adaptive methods (pureed food, mechanical altered diet, thickened or carbonated liquids, acidification of food, eating and drinking aids, counselling on eating behavior).

These methods are often used in combination [248]. In a comprehensive technical review of the American Gastroenterological Association, swallowing therapy was given a type C recommendation according to limited evidence of published studies [249]. In a Cochrane review on interventions for dysphagia in acute stroke a benefit of swallowing therapy could not be shown. This might be due to the small numbers of patients investigated [250]. Nevertheless, in an evidence-based systematic review of the Agency for Health Care Policy and Research (AHCPR), dramatic reductions in the occurrence of pneumonia were observed when a systematic program of diagnosis and treatment of dysphagia was implemented in an acute stroke management plan [251]. Further reports have shown efficacy of swallowing therapy or of single methods used in swallowing therapy on clinical relevant endpoints such as restoration of oral intake (class III evidence [252, 253]) or swallow scores which reflect activation limitations (class II evidence [254, 255], class III evidence [256, 257]). Only one single study exists on MS patients. It demonstrated that in mild and moderate dysphagia, aspiration observed by FEES could be avoided by swallowing therapy. This was not the case in severe dysphagia (class III evidence [258]). Recommendations on swallowing therapy in patients with MS are therefore based on expert opinion, plausibility of applied methods and therapeutic interventions in diseases other than MS [246, 259].

Invasive and Surgical Treatment

In some patients with pronounced and irreversible dysphagia, sufficient nutrition has to be maintained by a nasogastric/enteral tube or a percutaneous endoscopic gastrostomy (PEG), especially when a sufficient intake of food and fluids is impossible or severe aspiration has occurred despite conventional therapy [251, 260, 261].

Even if there are no sufficient data concerning MS patients, the results of nasoenteral or PEG feeding in other neurological disorders like amyotrophic lateral sclerosis (ALS) or stroke demonstrate its efficacy [250, 262, 263]. Nevertheless, application of this treatment for the individual patient has to be discussed responsibly [264]. Mild complications during insertion of a PEG may occur in 13–43% of patients, severe complications in 0.4–8.4%, the mortality reaching 0–2% where the type of disease, age, other risk factors all seem to influence outcome [260]. In patients who required tube feeding within the first 2 or 3 weeks of stroke, fatality and poor outcome were significantly higher for those who were fed via PEG than via a nasogastric tube (class I evidence [265]). After 4 weeks, however, nutrition via a PEG proved to be more effective compared to a nasogastric tube, but was associated with more adverse effects (class I evidence [266]). Therefore in patients with transient dysphagia who require tube feeding and in whom a rapid improvement can be expected, e.g. after an acute relapse, a nasogastric tube may be applied.

Unfortunately, available data do not show that feeding tubes reduce the risk of pneumonia in patients with neurogenic dysphagia [251, 267]. The offer for enteral tube feeding as prophylaxis against aspiration and pneumonia should be reserved to those patients who have developed recurrent pneumonia despite all efforts, whose coughing during meals is extremely uncomfortable and to the acutely ill with impaired consciousness [267]. In highly selected patients with recurrent pneumonia due to aspiration of saliva even a tracheotomy with a blocked cannula or other surgical interventions may be considered [249].

Drug Treatment

Pronounced hypersalivation may be attenuated using anticholinergic drugs [262] or by local injection of botulinum toxin A into the salivary glands as has been demonstrated in patients with ALS and Parkinson's disease [268–270]. Botulinum toxin A applied to the superior esophageal sphincter may reduce dysphagia due to an elevated sphincter tone [271].

Recommendations

- Functional swallowing treatment in patients with relevant dysphagia (type C recommendation).
 - For patients who require tube feeding for <3–4 weeks, nasogastric tubes should be used, for longer periods feed via percutaneous endoscopic gastrostomy (PEG) (type B recommendation).
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Epileptic Seizures

The prevalence of epileptic seizures in patients with clinically definite MS is estimated between 0.9 and 7.5% (normal adult population about 1%). Seizures may occur with relapsing or with chronic progressive MS and, moreover, may be part of a relapse as well. Tonic-clonic and complex partial seizures are likely to be the most common types. Even a status epilepticus has been reported. In rare cases, seizures were thought to be the first clinical event.

Specific Treatment

To our knowledge, no studies have been performed dealing with treatment of epileptic seizures, especially in patients with MS. Therefore, they should be treated according to generally accepted guidelines concerning choice of drug and indication for monotherapy and combination of drugs, respectively. Following the first epileptic manifestation, treatment should be initiated if the seizure is likely due to an MS lesion (e.g. juxtacortical or cortical) due to the high risk of seizure recurrence [272]. Only if the seizure has been associated with a relapse, antiepileptic drug treatment may be deferred until after seizure recurrence. Termination of antiepileptic drug treatment has to be weighed against since the risk of injuries following a seizure is considerably high.

Recommendations

- Initiation of antiepileptic drug treatment after a first epileptic seizure with a likely association to appropriate lesion sites except it has been part of an acute relapse (expert opinion).
 - Treatment regarding choice of drug, monotherapy or combination therapy according to existing guidelines.
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