

Symptomatic Treatment of Multiple Sclerosis

(Autorship has to be specified according to the collaborating MS societies)

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Introduction

Up to now several evidence-based treatment recommendations on immunomodulatory and immunosuppressive treatment of multiple sclerosis (MS) have been published, e.g by

- the Multiple Sclerosis Treatment Consensus Group (MSTCG), representing members of the Medical Advisory Boards from MS Societies of Austria, Germany and Switzerland [MSTKG 1999; MSTKG 2001; MSTKG 2002; MSTCG 2004]; these 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 additional 11 European countries [MSTCG 2004];
- the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines [Goodin 2002],
- the European Task Force of the European Federation of Neurological Sciences [Sellebjerg 2005].

These recommendations include evidence based knowledge and expert opinions where sufficient data from clinical trials are not yet available. Meanwhile these guidelines have shown 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 MSTKG from Austria, Germany and Switzerland 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 [MSTKG 2004]

and updated considering the specific literature until August 2006. The 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 [EMSP 2004] 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 not 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 anti-epileptic 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 centres 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 off-label drugs thus cutting these patients off from such treatment.

An important prerequisite for an effective symptomatic treatment is the adequate classification of symptoms. For example, there are different types of MS-related pain which have to be treated according to their 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. We hope that the national

agencies and insurance companies will accept consensus statements of this kind to allow reimbursement since 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 [Goodin 2002]).

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. For clinical purposes spasticity may be classified into a tonic (with persistently elevated muscle tone) and a phasic form (with intermittently elevated muscle tone) the latter often associated with painful cramps. In patients with severe and longstanding 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 compensate 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;
- information and training for appropriate posture, positioning and body transfer;
- amelioration of motor function;
- reduction of pain;
- 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 [Wiles 2001]. The most common techniques, e.g. those by Bobath, Vojta, Brunnstrom, and proprioceptive neuromuscular facilitation (PNF) appear to be of roughly equal efficacy, despite their different rationale [Paci 2003].

Passive treatment with an isokinetic apparatus was shown to lower spastic hypertonia in legs in patients after stroke [Nuyens 2002]. Moreover, treadmill training with partial body weight support, combined with Vojta –type physiotherapy, will reduce spasticity in MS patients [Laufens 1998]. Moreover, repetitive training of isolated movements may also reduce spasticity in a paretic hand [Bütefisch 1995].

There are other “passive” treatment modalities capable to lower 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 mobilisation of joints using motor-driven bicycles several times a day, and use of dynamic or static splints [McPherson 1985]. The transient beneficial effect of cooling on elevated muscle tone was well worked out [Mecomber 1971]. Hydrotherapy, too, has proven to reduce spasticity as well as the need for baclofen in patients with spinal cord injury [Kesiktas 2004].

Drug treatment

Spasticity can be ameliorated by antispastic drugs but their efficacy needs to be demonstrated by available scores. Unfortunately, these scores do not allow the assessment of the overall effects [Shakespeare 2003]. The drugs should be given in divided doses according to the degree and fluctuations of spasticity throughout the day, for example 30 to 45 minutes before getting up in the morning, with 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 oral antispastic drugs used most often are baclofen and tizanidine, and both particularly reduce “spinal spasticity”. For Tizanidine (2-24 mg/d p.o. [Smith 1994; Nance 1997]) and baclofen (10-120 mg/d p.o., [Sawa 1979; Brar 1991; Orsnes 2000]) sufficient evidence is available to support their use, whereas dantrolene and tolperisone were not tested appropriately and therefore are recommended as second line drugs. Patients undergoing antispastic treatment with these drugs often report reduced spasticity and spasticity-related pain or clonus, especially at night [Paisley 2002].

The strong antispastic effects of benzodiazepines are well substantiated, but their side effects including sedation and dependence limit their use in MS [Paisley 2002; Shakespeare 2003]. Gabapentin (300–3600 mg/d), which has been extensively studied in epilepsy and neuropathic pain syndromes, was shown to be effective in treating phasic spasticity [Cutter 2000; Mueller 1997]. 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 (CAMS), 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 [Zajicek 2003]. The latter observations have been confirmed in some smaller studies [Killestein 2002; Vaney 2004; Wade 2004]. Recently Zajicek and co-workers presented data of a 12 month follow-up period with the CAMS patients demonstrating a moderate positive effect of THC on the Ashworth scale, too, whereas in the placebo group spasticity increased gradually. Patients by themselves estimated that the cannabinoids were effective [Zajicek 2005]. Using low doses (1 mg per day) of nabilone, a synthetic cannabinoid, spasticity-related pain was significantly reduced in a small double-blind, placebo-controlled cross-over trial [Wissel 2006]. Nevertheless, based on the available evidence, the routine 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 addition to the treatment of spasticity, and may especially be of great value in reducing focal limb spasticity (e.g. of adductor muscles). Two randomised, placebo-controlled studies using the commercial preparations Botox^R [Snow 1990] or Dysport^R [Hyman 2000] demonstrated a significant reduction of spasticity in adductor muscles compared to placebo. With higher Dysport doses (1500 E) more adverse effects occurred compared to injections of 1000 E or 500 E [Hyman 2000].

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 [Penn 1989; Middel 1997]. Intrathecal baclofen results in a significant reduction of muscle tone, frequency of spasms and severity of pain [Boviatsis 2005] 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 rarely be severe and even life-threatening. Therefore continuous and skilled medical care in specialized centres is needed.

Intrathecal injection of corticosteroids (triamcinolone acetonide): This treatment has been performed in some MS centres since the 1980ties, 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 i.v. corticosteroids. There is only one recent follow-up study examining the effect of repeated intrathecal triamcinolone

injections (40 mg every 3rd day, up to six times). This treatment resulted in a significant improvement of the EDSS and of walking distance. Serious side effects were not observed [Hoffmann 2003]. 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
- If spasticity cannot be controlled sufficiently by physical therapy alone, baclofen or tizanidine should be used. Daily doses should be gradually increased, the maintenance dose should be adjusted according to the individual patient's course and severity of spasticity during the day. Gabapentin may be effective, too. 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. Continuous intrathecal baclofen infusion should be used only in cases with severe and otherwise uncontrollable spinal spasticity.
- Application of oral cannabinoids and of intrathecal triamcinolone acetonide outside prospective clinical trials should be restricted to centres with special experience.

Fatigue

At some stage during their disease, up to 75 % of MS patients suffer 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. Rise in body temperature 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 [Krupp 1989]) and the modified Fatigue Impact Scale (MFIS [Kos 2005]) which among themselves are only partially comparable [Flachenecker 2002]. Aims of treatment are the reduction of fatigue and the facilitation of normal activities in social and occupational life.

Specific treatment

The non-pharmacological treatment of fatigue includes structured “energy conservation” strategies, regular exercise programs as well as cooling or avoidance of hyperthermia, respectively. For drug treatment of fatigue amantadine, modafinil, 4-aminopyridine and – especially with concurrent depressive symptoms – antidepressants are used [MacAllister 2005]. Another mainstay of treatment is the treatment or avoidance of fatigue-aggravating factors like infections, anaemia, hypothyroidism, or medications.

Energy conservation strategies, physical training and multimodal rehabilitation

Energy conservation strategies consist of regular breaks throughout the day, effective communication, proper body mechanics, ergonomic principles, modification of the environment, setting priorities, activity analysis and modification, and living a balanced lifestyle [Finlayson 2005]. Structured courses lasting 6 weeks (2h/week) may result in a lower degree and impact of fatigue, as well as an amelioration of quality of life [Finlayson 2005; Mathiowetz 2005].

Aerobic training can improve subjective health and physical strength but does not affect fatigue scores significantly [Mostert 2002; Petajan 1996; Surakka 2004]. 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 [Patti 2002; Di Fabio 1998; Mathiowetz 2001]. Moreover, special Yoga exercises adjusted at common MS symptoms like spasticity or cerebellar tremor, seem to improve fatigue [Oken 2004]. Pulsed magnetic field therapy did not prove to be effective in reducing fatigue [Mostert 2005].

Cooling, lowering of body temperature

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 [Beenakker 2001], gait [White 2000] and also fatigue [Flensner 2002]. Cooling garments may result in a better Multiple Sclerosis Functional Composite (MSFC [Schwid 2003]). It can result in a distinct reduction of fatigue and may last from 30-45 minutes up to several hours. Studies on the practicability of using cooling garments in an outpatient situation are not yet available.

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 to 400 mg/day [Krupp 1995; Cohen 1989].

4-Aminopyridine, 3,4-Diaminopyridine: Aminopyridines have been investigated in some smaller double-blind studies. 4-aminopyridine (4-AP) seems to be superior to 3,4-diaminopyridine (3,4-DAP) in the amelioration of temperature-related MS symptoms [Polman 1994]. 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-aminopyridine. 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 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 [Rossini 2001]). Moreover, motor functions increase [Sheean 1998] and may result in an amelioration of the EDSS [van Diemen 1992]. A slow release formulation of 4-AP proved to reduce fatigue [Schwid 1997]. 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 [Weinshenker 1992].

L-Carnitine modulates mitochondrial metabolism of muscle fibers and is usually used to treat some metabolic muscle disorders. In MS-related fatigue, L-acetyl-carnitine led to amelioration of different fatigue scales in 29 % of patients compared to 21 % of patients receiving amantadine [Tomassini 2004]; up to now these results have not been confirmed by other authors.

Modafinil: This α -adrenergic drug has originally been developed for the treatment of narcolepsy. Some small open, single-blinded studies demonstrated a positive effect on fatigue (200 to 400 mg/day [Rammohan 2002; Zifko 2002]), whereas a recently published double-blind multicentre study revealed no significant differences in terms of the Modified Fatigue Impact Scale (MFIS) between treatment (200-400 mg/d over 5 weeks) and placebo [Stankoff 2005]. These results are at variance with the experience of others indicating that Modafinil may be effective. Moreover, some concerns regarding the study design of the Stankoff study were raised [Kraft 2005; Rammohan 2005]. In summary Modafinil (up to 200 mg/d am) seems to be effective in numerous patients suffering from pronounced daytime sleepiness. Major adverse effects include headache, dizziness, and agitation.

Further treatments: A small cross-over trial with aspirin 2 x 650 mg has recently shown some benefit on fatigue in MS [Wingerchuk 2005]. 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 [IFNB study group 1993; PRISMS 1998; Jacobs 1996]. Although in one other study the effect of β -interferons and glatirameracetate (GLAT) on fatigue was measured using the Fatigue Impact Scale. 24,8% of patients receiving GLAT reported a reduced degree of fatigue [Metz 2004].

Recommendations

- Exclusion of other treatable causes of fatigue like depression, infections, hypothyroidism, and sedatives
- Aerobic training, energy conservation training, multimodal rehabilitation
- Cooling of the body or of extremities.
- Drug treatment with amantadine (few adverse effects). If insufficient effect: Modafinil, 4-aminopyridine, (L-acetyl-carnitine).

MS-related pain syndromes

The frequency of clinically relevant pain is reported by up to 86% of MS patients. 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 dysaesthesia and paraesthesia; thalamic pain
- **Pain as indirect sequel of other MS symptoms:** Joint and muscle related pain due to long standing 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 beta-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.

Most evidence-based studies on pain treatments used today in MS-related pain syndromes have been investigated in neuropathic and nociceptive pain resulting from other diseases than MS. 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 are indicated [MSTCG 2004] and are known to reduce 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“ dysaesthesias 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/d) or antiepileptic agents like carbamazepine (200-1600 mg/d [Sindrup 2000]). Similar effects can be achieved with gabapentin (300-2400 mg/d [Houtchens 1997]) and lamotrigine (200-400 mg/d [Backonja 2003; Eisenberg 2001]) or pregabalin (150-600 mg/d [Rosenstock 2004; Sabatowski 2004]). Neuropathic pain in MS patients has been ameliorated, too, by topiramate (200-300 mg/d [d'Aleo]).

If opioids are used in treatment escalation for central pain, high dosages are required in most cases [Kalman 2002] and will therefore not be tolerated by many on long term treatment, e.g. morphine 9-30 mg/d [Attal 2002].

Serotonin-reuptake inhibitors (SSRI's) appear not as effective as tricyclic antidepressants [Sindrup 2000] in reducing pain. Newer antidepressants [Mattia 2002] like mirtazapine which indirectly enhance noradrenergic and serotonergic transmission, the dual serotonin-noradrenalin reuptake inhibitors venlafaxin [Grothe 2004; Sindrup 2003] und duloxetine [Iyengar 2004] as well as the noradrenalin reuptake inhibitor reboxetine [Schüler 2002] 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 [Zajicek 2003]. Unfortunately the type of pain had not been described in detail. In another study dronabinol (3 weeks, up to 5 mg twice daily) proved to be more effective in the treatment of MS-related central pain than placebo thus being considered to be of clinical relevance [Svendsen 2004]. These results have been widely confirmed using a whole-plant cannabis-based extract [Rog 2005]. In 2005, Sativex[®], a cannabis-based drug for the treatment of MS-related pain that has to be administered via a spray into the mouth, was approved in Canada.

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,
- (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 wheel-chair bound patients. In these cases therapeutic exercises with “proprioceptive re-education” is recommended for reduction of pain [Philadelphia Panel Shoulder Pain 2001]. Manual therapy with spinal mobilisation seems to be superior to conventional physiotherapy [Korthals-de Bos 2003]. Shoulder pain may be alleviated convincingly by ultrasound treatment for calcified tendinopathy [Philadelphia Panel Shoulder Pain 2001].

Drug treatment of these pain syndromes should follow published guidelines for therapy of degenerative arthropathies since no MS-specific studies exist [Eccles 1998].

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, wheel chairs, 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 beta interferons or glatirameracetate 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 [Rio 2004; Reess 2002]. Increasing headache during beta 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: immobilisation, muscle tenseness, spasticity of truncal muscles, osteoporosis, chronic degenerative disc disorders and vertebral joint disease. Again, physical therapy to optimise 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 [Philadelphia Panel Low back pain 2001] as well as acupuncture massage which was claimed to be superior to conventional massage [Furlan 2001]. Drug treatment should be performed according to that for chronic neck and shoulder pain [Eccles 1998].

Lumbar, pelvic and iliosacral pain often are pseudoradicular in origin. In radicular pain, disc herniation should be looked for. In osteoporosis, biphosphonates are the treatment of choice [Gangji 1999]. 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.
- For painful dysaesthesias and neuropathic pain: Amitryptiline or carbamazepine, alternatively gabapentin, lamotrigine or pregabalin in gradually increasing doses.
- For arthralgias, neck and shoulder pain: Education and treatment on the role of abnormal posturing, optimization of mechanical aids. Individually supervised physiotherapy. Drug treatment following published guidelines.
- For flu-like symptoms and muscle pain during beta interferon therapy: acetaminophen (paracetamol) or other NSAID, for local pain cold packs. For increasing headache drug treatment following published guidelines of the national headache societies.
- For low back pain: after excluding root or cord compression, physiotherapy. Drug treatment following published guidelines.
- Newly appearing pain should be diagnosed and should not be attributed „automatically“ to MS. In most cases a long standing and multidisciplinary treatment is necessary.

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 few patients it will be the sole clinical complaint.

Detrusor overactivity with restricted storage capacity, urgency, increased frequency of micturition, and incontinence is the most common type 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 overactivity with an obstructive component and the risk of 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, microbiological 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 septicaemia, 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/d) but not late at night because of nocturia, and, if a pathological residual volume is present, not to delay micturition in case of urgency [de Ridder 2005]. Bladder training [Roe 2000; Subak 2002] as well as toilet training [Eustice 2003] both seem to be effective. Moreover, counselling on aids like insets, condom urinals or other devices to treat incontinence is useful.

Physiotherapy:

Basic treatment modalities like pelvic floor training, electromyographic feedback training and neuromuscular electrical stimulation are used only sporadically. In female patients suffering from MS, the combination of these three treatments proved to be superior to just pelvic floor training in terms of the number of leaks and the 24h pad tests [McClurg 2006]. Combined pelvic floor training and electrical stimulation in MS patients with low residual volume will reduce micturition frequency, urgency and incontinence, especially in men [Vahtera 1997]. Biofeedback and pelvic floor training may lead to a reduction of urgency and incontinence without normalisation of urodynamic parameters during treatment [Hay-Smith 2002; Nygaard 1996]. Nevertheless even pelvic floor training alone may result in a 67 % reduction of incontinence events, independent of supine or upright body positions during exercise [Borello-France 2006].

Drug treatment

Drugs to reduce detrusor overactivity: Anticholinergic compounds: The positive effect of oxybutynin and tolterodine to reduce incontinence and urgency in overactive bladder has been proven in several studies [Hay-Smith 2002; Drutz 1999; Cardozo 2000; Jacquetin 2001; Stöhrer 1999]. The anticholinergic side effects may be attenuated by symptomatic treatment, slow release formulations, or a newly developed oxybutynin-containing matrix transdermal adhesive [Chancellor 2001]. Trospiumchloride (40-60 mg/d) is comparable to oxybutynin, but may cause fewer anticholinergic side effects. Propiverin (45 mg/d) has a positive effect on detrusor overactivity and has also fewer anticholinergic effects than oxybutynin. Adverse effects on the CNS seem to be less pronounced with trospiumchloride or tolterodine than with oxybutynin [Todorova 2001]). The new anticholinergic agents darifenacin [Chapple 2004a] and solifenacin [Cardozo 2004; Chapple 2004b] may reduce urgency, micturition frequency and incontinence effectively. It should be stated that mostly non neurogenic patients have included into the studies mentioned here. Patients with MS were often excluded. Therefore, there is an urgent need for more specific trials in patients with MS. The alpha-blocking agents alfuzosine and tamsulosine aim at reducing an elevated voiding obstruction of the bladder especially in patients with simultaneous detrusor overactivity. Tamsulosine (0,4 resp. 0,8 mg once daily) improves storage capacity and emptying of the bladder [Abrams 2003]. Antispastic agents: Baclofen has a positive effect in spastic or dyssynergic sphincter when given orally [Taylor 1979; Steers 1992]. Because of its common systemic side effects, baclofen is only a second-line drug for treatment of overactive bladder unless low doses are effective.

A reduction of episodes of urge incontinence may also be achieved by administration of Δ^9 -tetrahydrocannabinol (THC) or a cannabis extract. In an open-label pilot study of cannabis-

based extracts, the number and volume of incontinence episodes and the frequency of nocturia decreased significantly [Brady 2004]. Similar findings could be demonstrated in a substudy of the CAMS trial (see sections on spasticity and pain), where both active treatments showed significant effects over placebo in the adjusted episode rate of urge incontinence [Freeman 2006]. Nevertheless the drug has not yet been approved for treatment of NBD and should be tried only by experienced physicians.

Desmopressin, the antidiuretic hormone, effectively reduces nocturnal micturition frequency [Hoverd 1998; Valiquette 1996] and may be helpful for patients attending social activities like visiting a theatre or concert. Desmopressin should only be given to patients with normal heart and kidney function. Dose should not exceed 20 µg intranasally [Eckford 1995], then treatment is mostly free of side effects [Tubridy 1999]. In a recent meta-analysis a moderate effect of desmopressin on nocturia in people with MS could be demonstrated; the number of voids during the night, and the urine volume within 6h after intake were reduced [Bosma 2005].

Treatment of acute bladder infection: In patients with NBD bladder infections are common and should be treated with targeted antibiotics [Naber 2001] 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 leucocyturia, elevated white blood cells as well as erythrocyte sedimentation rate and C-reactive protein may help to make the diagnosis. Due to the shorter resting time of urine within the bladder, the nitrite test may be falsely negative even when nitrite secreting bacteria are present.

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 [Sauerwein 2002]. For prophylaxis of infection, methenamine (2x1 g/d [Banovac 1991]) and methionine (3x500 mg/d [Fünfstück 1997]) can be used whereas the efficacy of cranberry juice is questionable. (*Prof. de Ridder: Methionine and methenamine are not available in Belgium anymore. Nitrofurans could be a valuable alternative. They have continued to be active against a wide spectrum of common urinary tract pathogens and are well tolerated [Guay DR: An update on the role of nitrofurans in the management of urinary tract infections. Drugs 2001; 61: 353-64]*). The most important risk factor for complicated bladder infections is a transurethral or suprapubic catheter. In these patients methenamine is not helpful because of its mechanism of action. Even in acidic urine (pH<6) it will take 30 to 90 minutes to release inhibitory concentrations of formaldehyde. Vitamin C has not shown to be effective [Castello 1996]. The frequency of symptomatic bladder infections could not be reduced by chronic administration of Cotrimoxazol [Mohler 1987].

The value of long-term antibiotic treatment is still debated [Morton 2002] since this is likely to provoke selection of drug-resistant bacteria.

Invasive treatments: Intermittent aseptic catheterisation with disposable catheters done 4 to 6 times/d is the treatment of choice in a hyperreflexive bladder with obstruction, but may also be effective in hypo/areflexive NBD [Oakeshott 1992]. Bacterial infection remains a risk and small skin or mucosal bleedings may occur.

In MS patients self catheterisation 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 [Wyndaele 2002]. Disposable catheters with integrated lubricants should be preferred when available. Intermittent aseptic catheterisation combined with drug-induced attenuation of the detrusor may be more effective than bladder emptying by trigger manoeuvres, abdominal press or Credé manoeuvre with regard to long time prognosis [Giannantoni 1998].

Intravesical treatment: In case of severe adverse effects of oral anticholinergics these and other drugs such as vanilloids capsaicine or resiniferatoxin may be administered directly into the bladder. Oxybutynin [Lehtoranta 2002] and trospiumchloride [Fröhlich 1998] 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 catheterisation.

The positive effect of intravesical capsaicine in patients with detrusor overactivity could also be demonstrated in several studies [de Seze 1998]. Unfortunately instillation is extremely painful. Resiniferatoxin is equally effective and causes much less pain [Giannantoni 2002]. 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 vesico-ureteral reflux, stone formation, or bladder carcinoma, indwelling transurethral catheters should 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 overactivity 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 [Morton 2002].

Botulinum toxin A: In a trial with 231 patients with neurogenic detrusor hyperactivity, injection of 300 MU botulinum toxin type A led to an unequivocal amelioration of bladder capacity, reflex volume, and average micturition pressure [Reitz 2004]. Intravesical administration seems to be safe and results in a significant reduction in the daily frequency of urinary

incontinence episodes in patients with neurogenic detrusor overactivity [Gallien 2005; Schurch 2005; Schulte-Baukloh 2006] lasting for up to 9 months. Doses used were 100 or 300 U Botox® or 500 to 1000 U Dysport®, although the optimal dose still has to be defined [Ruffion].

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 [Chartier-Kastler 2000]. Nevertheless, this treatment should be restricted to very experienced and specialised centres. 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.
- Counselling for adequate fluid intake; information on incontinence devices, acidification of urine with methionine or cranberry extract.
- 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; drugs to diminish detrusor overactivity include trospiumchloride or tolterodine, oxybutynin, propiverine, solifenacin, darifenacin; electrostimulation at S3 root level.
- If obstruction with or without urgency is present, urodynamometry, initiation of treatment is recommended in cooperation with an urologist. In most cases: treatment with anticholinergic drugs combined with intermittent sterile catheterisation may be of some value.
- In detrusor overactivity resistant to oral anticholinergic drug treatment injection of botulinum toxin type A seems to be effective and safe.
- Recurrent bladder infections: Counselling on specific causes, optimisation of symptomatic treatment, methionine, in severe cases combined with methenamine; avoidance of chronic antibiotic treatment.
- Severe nocturia: desmopressin 20 µg intranasally.

- Long-term catheterization and surgery is recommended only in treatment-resistant cases because of its irreversibility, late complications and unpredictable course of the disease.

Neurogenic bowel dysfunction

Disturbances of bowel function like constipation and/or incontinence will occur in about 70% of MS patients. Especially constipation may often worsen some other MS symptoms such as neurogenic bladder dysfunction and spasticity. 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 and of 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 [Wiesel 2001]. The benefit of pelvic floor training has so far never been elucidated [Norton 2000]. Faecal incontinence in women with weak pelvic floor muscles may be ameliorated partially by electrical stimulation [Hosker 2000]. There are treatment trials providing sufficient data on the use of laxatives, drugs augmenting bowel motility, and botulinum toxin A [Wiesel 2001; DasGupta 2003]. The established guidelines are likely to be applicable also in MS patients.

Recommendations

In case of prevailing constipation(

- Sufficient fluid intake (1,5 – 2 L/day), nutrition rich in dietary fibre.
- Physiotherapy (standing devices, motor-driven bicycles, colon massage).
- Pelvic floor training for relaxation of sphincter muscles, biofeedback.
- In case of hardened faeces lactulose or macrogol is recommended except if faecal incontinence is also present.
- Facilitation of rectal emptying by glycerine suppositories or rectal filling with fluids.

- In single cases: targeted utilisation 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 of 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 faecal incontinence

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

Sexual dysfunction

Sexual dysfunction does not only represent a problem of the individual patient but may also lead to major 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 frequent, 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..

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 %). Neurogenic 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 normalise 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 beta blockers. MS symptoms which may impair sexual intercourse like adductor spasticity, bladder infection or incontinence should be treated appropriately. Counselling by an experienced specialist and psychotherapy may be of some value [Foley 2001].

Drug treatment

The phosphodiesterase-5-inhibitor sildenafil is now the most intensively studied drug for ED [Landtblom 2006]. 25 to 100 mg of sildenafil should be taken orally 1 hour 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 [Fowler 2005]. 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 to duration of effect and adverse events but there are no studies available.

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 minutes after ingestion. Up to 6 mg will lead to a significant better erection compared to placebo [Dula 2000]. 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 supposed non-neurogenic ED, yohimbine may ameliorate erection [Vogt 1997].

In female patients with reduced lubrication and resulting dyspareunia treatment with tibolone, estrogen-containing unguents, or commercially available lubricant creams can be recommended [Laan 2001; Davis 2002]. After treatment with sildenafil a positive effect on lubrication could be demonstrated in only a few female MS patients [Dasgupta 2004].

Invasive and surgical treatments, aids

After the introduction of sildefanil 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 [Godschalk 1994; Linet 1996]). Transurethral application is also possible [Padma-Nathan 1997]. 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 [Lewis 1997]. Penis prostheses offer a further treatment option [Evans 1998].

Recommendations

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

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 [Trouillas 1997; Albrecht 1998]. 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 [Jones 1996]. 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 [Meshack 2002] 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 minute) local application of ice [Albrecht 1998]. In another comparative study using cooling cuffs (skin temperature 18° vs. 25° Celsius) a temperature-correlated effect on postural tremor could be demonstrated [Feys 2005]. 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 beta blockers can be used additionally in patients with severe intention tremor.

A clear benefit of beta blockers could only be demonstrated in essential tremor whereas propranolol was not effective in patients with cerebellar tremor [Koller 1984]. Besides this some patients apparently may profit from treatment with beta 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 [Sechi 1989] as well as topiramate [Sechi 2003] may positively influence cerebellar tremor.

Other drugs: Clonazepam (3-6 mg/d) may be of some benefit in cerebellar tremor, too [Trelles 1984]. The effect of Oxitriptan (5-hydroxytryptophane) on ataxia of the trunk and legs usually occurs only after treatment with 3x300 mg/d over about 6 weeks [Trouillas 1988]. 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 [Gbadamosi 2001; Bier 2003], whereas intravenous ondansetron (8 mg/d) caused a clear short lasting amelioration of writing ataxia and of the patients' subjective impression [Rice 1997].

Isoniazid has been used in patients with cerebellar tremor with conflicting results [Koller 1984; Hallett 1985]. Adverse effects may limit treatment. Physostigmine has no significant effect on cerebellar tremor [Duquette 1985; Wessel 1997].

Surgical treatment

With stereotactic operations, e.g. VIM thalamotomy and VIM (deep brain-) stimulation, reduction of tremor could be demonstrated though [Bittar 2005] 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 [Wishart 2003]. Simultaneously the level of disability and SF-36 subscales remained largely unchanged [Hooper 2002; Berk 2002]. 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 [Alusi 2001]. If stereotactic treatment is considered, the patients' disease course should be stabilized by effective immunotherapy for at least one year.

Recommendations

- Regular physiotherapy and occupational therapy, cooling.
- In patients with predominant tremor: additional drug treatment (monotherapy) with a beta blocker (rapid assessment of efficacy) and, if not successful, monotherapy with carbamazepine, primidone or clonazepam. If escalation is necessary combination therapy with a beta blocker and an antiepileptic drug. Efficacy of these drugs is often limited by their extensive adverse effects.
- If tremor is unresponsive to combination therapy: oxitriptan

- Only in patients with considerable tremor unresponsive to drug treatment or with severe side effects electrical stimulation of the thalamus should be considered .

Cognitive dysfunction

Dysfunctions of cognitive skills of some degree may affect up to 70 % of patients with MS and may lead to substantial restriction of their intellectual abilities and psychological drive. MS patients mostly suffer from dysfunctions in memory, attention, processing of information, restrictions in visuospatial and visuoconstructive abilities and cognitive flexibility [Calabrese 2006] whereas implicit functions and speech are rarely disturbed. The patients' perception of his/her cognitive dysfunction is often inadequate or even missing [Goverover 2005] and this was originally meant by the term "euphoria".

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

Specific treatment

Treatment should be aimed at specific techniques to reduce the cognitive dysfunctions present in the patient. Important goals are the repair of function, cognitive reorganisation, external aids and environmental actions. This may include behavioural coping strategies, as well as disability-specific computer training programs. Drug treatment with anticholinesterases, especially donepezil, seems to be of limited value to treat deficits in verbal learning and memory [Christodoulou 2006; Krupp 2004]. Progression of cognitive dysfunction may be partly prevented by effective immunomodulatory treatments, e.g. beta-interferons and glatiramer acetate [Amato 2006].

Attention training

Nowadays PC-based techniques are frequently used to treat permanent and selective alertness or activation of alertness [Niemann 1990; Plohmann 1998; Wood 1987]. 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 severe affected patients memory aids and training of memory strategies may be helpful, whereas severely affected patients usually need memory aids like notebooks and reminders, e.g. "NeuroPage [Mendozzi 1998;

Freeman 1992; Wilson 1997]. 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 [Chiaravalotti 2005]. The benefit of simple tasks such as cross-word riddles, puzzles or other games training memory skills is probably more aspecific and helps maintaining some attentional functions.

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 [Benedict 2000; Jonsson 1993; Mendoza 2001].

Drug treatment

So far donepezil and amantadine have been studied with respect to their effect on cognitive dysfunction. Moreover there are some data suggesting a slowing of cognitive decline during immunomodulatory treatment of MS with beta interferons and glatirameracetate.

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 (10 mg/d [Krupp 2004; Greene 2000]).

In severely disabled MS patients, the amplitudes of cognitive evoked potentials could be improved with amantadine but reaction time measurements did not [Sailer 2000]; the clinical significance of these findings has to be determined [Geisler 1996].

Beta interferons, glatirameracetate: During treatment with beta interferon 1b the visuospatial performance in treated patients was stable compared to deterioration of this task in patients on placebo [Pliskin 1996]. Similar results have been achieved during interferon beta-1b treatment with respect to alertness, concentration, visual learning and recognition [Barak 2002]. On the contrary, another study using the same interferon in patients with relapsing-remitting MS failed to show any improvement of verbal memory [Selby 1998].

In a post-hoc evaluation of a study using beta interferon-1a significant differences with respect to information processing, memory, visuospatial and executive functions could be demonstrated after two years of treatment compared to placebo [Fisher 2000].

Studies using glatirameracetate [Weinstein 1999] or methotrexate [Goodkin 1992] could not detect any improvement or even stabilization of cognitive dysfunction.

Recommendations

- Patients and their family should be informed about cognitive dysfunction based on examples or situations of their daily life. This helps patients to become an active participant in the treatment process.

- Training should be aimed specifically at the disturbed cognitive function(s) and the impact of this/these on the handicap. High frequency treatment is mandatory.
- Complex neuropsychological treatment is preferable, e.g. treatment of simultaneous depression, relaxation techniques, counselling within multimodal rehabilitation.
- With immunomodulatory treatment cognitive decline may be delayed.

Depression

Depressive syndromes occur in about 50% of MS patients [Chwastiak 2002] demonstrating the need for rigorous treatment of this condition, especially in light of the high rate of attempted and completed suicides. Depression may also restrict the ability of a patient to adhere to a treatment; hence it is important to treat depression to ensure the patients better help themselves manage the disease. The diagnosis of depression, which may be complicated by other MS symptoms like fatigue and cognitive disturbance, requires careful differential diagnosis. Episodic fluctuations of depressive mood or difficult coping have to be distinguished from long-term depressive states and “organic” major depression. Even bipolar affective psychoses in MS patients are present twice as much as in normal population [Schiffer 1990]. Goals of treatment are the reduction of depressive mood by proper guidance and drug treatment when needed, and prevention of suicide. Even if beta interferons were not convincingly shown to cause depression [Zephir 2003; Kappos 2006] one should be alert in any patient at any time since in every day neurological practice some patients have been repeatedly reported to develop depression with the initiation of beta interferon treatment.

Specific treatment

Counselling

As depression is often masked by somatic 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 [Schwartz 1999].

Psychotherapy

Several studies demonstrate the efficacy of psychotherapy for depression in MS patients [Crawford 1985; Mendoza 2001; Mohr 2001; Mohr 2005]). Mainly cognitive behavioural therapy, that emphasizes active coping strategies with the disease, 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 serotonin reuptake inhibitors (SSRI) in depressive patients with other medical illness [Gil 2003]. Treatment with desipramine combined with psychotherapy [Schiffer 1990], with sertraline and psychotherapy [Mohr 2001], and with the monoaminoxidase (MAO) A inhibitor moclobemide [Barak 1999] is effective. The choice of drug used should be adapted to the other symptoms of the patient and to the treatments, as each drug may cause unwanted side-effects like sexual dysfunction (SSRIs) or increased fatigue (mirtazapine [Feinstein 2003]).

Recommendations

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

Paroxysmal symptoms

About 10 to 20 % of MS patients suffer from paroxysmal symptoms like trigeminal neuralgia (TN) and several other paroxysmal painful, sensory and – more rare – motor symptoms (Table 1). These are very short stereotype 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.

Table 1: Paroxysmal symptoms in multiple sclerosis

- Trigeminal, glossopharyngeal and other neuralgias (including MS-associated (pseudo-) radicular pain)
- Sensory symptoms: paraesthesias, dysaesthesias, Lhermitte's sign, pruritus,
- Paroxysmal ataxia and dysarthria
- Dyskinesias: paroxysmal dystonia (formerly: tonic brain stem seizures), hemispasmus facialis, tremor, akinesia (loss of muscle tone, kinesigenic 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

The diagnosis is made on clinical findings and should be completed by the documentation of frequency, localisation, 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 antiepileptic 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 [MSTCG 2004]. 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 [Wiffen 2000]. Nevertheless even in sufficient dosage carbamazepine may cause a paradoxical increase of some MS symptoms in single patients [Ramsaransing 2000; Leandri 2000]. Phenytoin, baclofen [Fromm 1984], lamotrigine (up to 400 mg/d [Zakrzewska 1997]), gabapentin (up to 1600 mg [Solaro 2000; Yetimlar 2004]), topiramate (up to 300 mg/d [Solaro 2001]), 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 i.v.. The efficacy of lamotrigine could be demonstrated even when combined with carbamazepine [Sindrup 2002]. 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/d [DMKG Study Group 2003]).

Surgical treatment

Surgical interventions, like thermocoagulation and glycerol instillation into the Cavum Meckeli are widely accepted as second line therapies for TN [Patwardhan 2006]. Microvascular decompression of the trigeminal nerve has been performed successfully even in single MS

patients [Broggi 1999], 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 dysaesthesias in only 10% of patients. 75% of patients will remain free of pain even after 3 years. Unfortunately there are no data on long time success compared to other surgical techniques [Kondziolka 2002]. 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 [Cheng 2005].

Other paroxysmal symptoms

Paroxysmal paraesthesias 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 to 300 mg may lead to complete relief of the symptoms treated. Gabapentin (up to 1200 mg/d [Solaro 1998]), Lamotrigine (up to 400 mg/d [Cianchetti 1999]), 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 [Blakeley 2002; Sakurai 1999].

Patients with Uhthoff's phenomenon should be told to avoid heat and to use cooling techniques. Moreover 4-aminopyridine may be of some value [van Diemen 1992]. The treatment of choice in the rare facial hemispasm is the application of botulinumtoxin A once this becomes disabling [Cakmur 2002].

Recommendations

- In most cases paroxysmal symptoms respond to treatment with carbamazepine . If paroxysmal symptoms newly occur with an acute relapse, a high dose steroid treatment according to established guidelines should be introduced.
- 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.
- For paroxysmal motor symptoms (spasm or myoclonus) treatment with clonazepam.
- In patients with drug-resistant TN: Consider thermocoagulation or instillation of glycerol into the cavum Meckeli, alternatively microvascular decompression or radiosurgery may be recommended.

Oculomotor symptoms

During the course of the disease about 30 to 50% of MS patients will suffer from oculomotor symptoms and in about 15% they may be part of the first attack. 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 i.v. methylprednisolone. An eye patch may be helpful during the acute phase to avoid double vision.

For drug treatment of pendular nystagmus gabapentin (900-1200 mg/d [Averbuch-Heller 1997; Bandini 2001]) or memantine (40-60 mg/d [Starck 1997]) should be used [Shery 2006]. Scopolamine adhesives, vigabatrin or baclofen are not effective.

Baclofen (3x5 mg per day) may reduce upbeat/downbeat nystagmus [Dieterich 1991]. A single dose of 3,4-diaminopyridine (3,4-DAP, 20 mg) will ameliorate downbeat nystagmus of different aetiologies [Strupp 2003]. There are no data concerning 3,4-DAP treatment in MS patients with downbeat nystagmus. 4-aminopyridine has been successfully used so far in two patients [Glasauer 2005; Kalla 2004].

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.
- For upbeat/downbeat nystagmus baclofen is the drug of first choice, for downbeat nystagmus 3,4-DAP may be used.
- In internuclear ophthalmoplegia drug treatment is rarely needed.

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 [Hartelius 2000; Yorkston 2003] 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 [Yorkston 2003]. 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%) [Darley 1972]. 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 [Samar 1988], the Frenchay Dysarthria-Examination [Enderby 1996], the Voice Handicap Index (VHI [Jacobson 1997]) or the Voice-Related Quality of Life Index (V-RQOL [Hogikyan 1999]). Goals of treatment are the restoration of lost speech functions and thus of the ability of unimpaired communication.

Specific treatment

Speech therapy is indicated at the latest when 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. Nevertheless some speech therapists prefer to start treatment even earlier.

Treatment should be performed by a team comprising a neurologist, an oto-rhino-laryngologist 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 [Spencer 2003]. Techniques to modify speech behaviour, 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 behavioural 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. Bobath 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) [Yorkston 2003; Spencer 2003]. 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 [Merson 1998; Miller Sorensen 2000]. 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 [Deane 2001; Deane 2002; de Swart 2003]. 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 [Sapir 2001]. However fatigue can interfere with results when this technique is used in MS patients. 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 [Yorkston 2003].

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 [Vogel 1987].

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 techniques, 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” [Yorkston 2003].

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 [Duffy 2003]. Additional training may enhance the positive effect of Botulinum toxin A treatment [Blitzer 1998; Duffy 2003]. In MS patients there is very limited experience [Rontal 1999].

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 [Friedrich 2001] and velopharyngeal surgery can be considered if a velum prosthesis is not effective [Yorkston 2001]. 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 [Hanson 2004]. 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 utilised even by patients suffering from severe motor impairment [Glennen 1997; Miller Sorensen 2000].

Before these more demanding aids are introduced to MS patients their cognitive, motor, visual and acoustic skills should first be checked and the acceptance, which often is a problem, of the patients and his interlocutor be considered [Hanson 2004]. A longer learning period is to be expected in an advanced MS patient than in an otherwise healthy language skills disorder.

Recommendations

- Speech therapy in patients with relevant dysarthria.

- Co-treatment of associated symptoms, e.g. fatigue, spasticity, tremor.
- Speech supplementation techniques und communication aids in patients with severely impaired understandibility despite speech therapy.

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 relative hypersialorrhea. 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 oto-rhino-laryngological examination and a functional swallowing test. A videofluorographic swallowing study (VFSS) and/or transnasal fiberoptic endoscopic examination of swallowing (FEES) may help in establishing the severity of dysphagia and the need for further treatment.

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 [McHorney 2002]. 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/manoeuvres) and
- adaptive methods (pureed food, mechanical altered diet, thickened or carbonated liquids, acidification of food, eating and drinking aids, counselling on eating behaviour).

These methods are often used in combination [Prosiegel 1999]. 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 [Bath1999].

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 [APHCR 1999]. 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 [Schurr 1999; Huckabee 1999] or swallow scores which reflect activation limitations [Freed 2001; Shaker 2002; Prosiegel 2002; Crary 2004].

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 [Calcagno 2002]. 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 [Prosiegel 2004; The National Collaborating Centre for chronic Conditions 2004].

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 [Löser 1996; AHCPR 1999; Eisen 2002].

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 [Miller 1999; Norton 1996; Bath 1999]. Nevertheless, application of this treatment for the individual patient has to be discussed responsibly [Sanders 2002]. Mild complications during insertion of a PEG may occur in 13 to 43 % of patients, severe complications in 0,4 to 8,4 %, the mortality reaching 0 to 2 % where the type of disease, age, other risk factors all seem to influence outcome [Eisen 2002]. In patients who required tube feeding within the first 2 or 3 weeks of stroke, fatality and poor outcome was significantly

higher for those who were fed via PEG than via a nasogastric tube [The FOOD Trial Collaboration 2005]. 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 [Park 1992]. 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 [AHCPR 1999; Finucane 1996]. 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 [Finucane 1996]. In highly selected patients with recurrent pneumonia due to aspiration of saliva even a tracheotomy with a blocked canula or other surgical interventions may be considered [Cook 1999].

Drug treatment

Pronounced hypersalivation may be attenuated using anticholinergic drugs [Miller 1999] or by local injection of botulinum toxin A into the salivary glands as has been demonstrated in patients with ALS and Parkinson disease [Ellies 2002; Giess 2000; Ondo 2004]. Botulinum toxin A applied to the superior oesophageal sphincter may reduce dysphagia due to an elevated sphincter tone [Chiu 2004].

Recommendations

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

Epileptic Seizures

The prevalence of epileptic seizures in patients with clinical 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 [Engelsen 1997]. 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 ictogenic lesion sites except it has been part of an acute relapse.
- Treatment regarding choice of drug, monotherapy or combination therapy according to existing guidelines.

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