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Tremor in multiple sclerosis

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■ **Abstract** Tremor is estimated to occur in about 25 to 60 percent of patients with multiple sclerosis (MS). This symptom, which can be severely disabling and embarrassing for patients, is difficult to manage. Isoniazid in high doses, carbamazepine, propranolol and gluthetamide have been reported to provide some relief, but published evidence of effectiveness is very limited. Most trials were of small size and of short duration. Cannabinoids appear ineffective. Tremor reduction can be obtained with stereotactic thalamotomy or thalamic stimulation. However, the studies were small and information on long-term functional outcome is scarce. Physiotherapy, tremor reducing orthoses, and limb cooling can achieve some

functional improvement. Tremor in MS remains a significant challenge and unmet need, requiring further basic and clinical research.

■ **Key words** multiple sclerosis · treatment · tremor · ataxia

Search strategy and selection criteria

References for this review were identified from searches of Pubmed (from 1966 to 2005) and the Cochrane Library (2005, Issue 2) with the search terms “multiple sclerosis”, “tremor”, “ataxia”, “disability”, “prevalence”, “surgery”, “thalamotomy”, “deep brain stimulation” and “treatment”. Articles were also identified through searches of the reference tables of identified papers. Furthermore we searched the ISI Science Citation Index for relevant articles citing identified papers. Only articles in English and German

were included in the review; publications in abstract form were not considered.

Introduction

Tremor is such a common problem in multiple sclerosis (MS) that the famous French neurologist Charcot (1825–1893) described it as a part of his triad of characteristic symptoms in MS, together with nystagmus, and scanning speech.

Tremor of the upper limbs can be very disabling and seriously impair many activities of daily living

and quality of life. In practice the treatment of tremor in MS is often frustrating. In this review we discuss medical, surgical and other treatment options.

■ Epidemiology

Although the epidemiology of symptoms in MS has been studied extensively, it remains difficult to ascertain the prevalence of tremor in historic study populations, mostly because Kurtzke's functional systems scale for cerebellar function, which is most widely used in clinical studies in MS, does not record tremor [55]. In a large long-term follow-up study, Weinshenker and colleagues found functionally relevant cerebellar deficits in one third of 259 patients [94]. In another study, disability and dependency of patients with MS were shown to correlate with the severity of ataxia [95].

Two newer studies assessed the prevalence of tremor in MS. One study by Alusi and coworkers examined 100 patients randomly selected from a London MS-clinic and found tremor in 58% of patients. The tremor was minimal in 27%, mild in 16% and moderate to severe in 15% of all patients [6]. As patients were selected from a specialist clinic, the relatively high prevalence and severity of tremor might be due to selection bias.

In a prevalence cohort study by Pittock and colleagues, 200 MS patients living in Olmsted County, Minnesota, USA were assessed for tremor and measures of disability. Tremor was found in 25.5% and severe tremor in 3% of the study population [74]. Probably the community based population in the latter study gives a more realistic estimate of tremor prevalence in MS. In both studies, however, tremor was associated with greater disability as measured on the expanded disability status scale (EDSS). In the Olmsted County population, patients with tremor of any severity were more likely to be unemployed or retired early because of disability.

■ Tremor subtypes

Tremor in MS can involve the head, neck, vocal cords, trunk and limbs, whereas involvement of the tongue, jaw or palate has not been reported [5].

The different types of tremor are currently classified according to a working consensus of the Movement Disorder Society [29]. In MS, the two most prevalent tremor forms are postural tremor (tremor present whilst voluntarily maintaining a position against gravity) and intention tremor (tremor occurring during target directed movement where tremor amplitude increases during visually guided movements towards the target). True rest tremor (tremor

Table 1 Details of the two main prevalence studies on tremor in MS

	London [6] (n = 100)	Olmsted County [74] (n = 200)
Total patients with tremor	58 (58%)	51 (25.5%)
Patients with severe tremor	15 (15%)	6 (3%)
Arm tremor	56 (56%)	47 (23.5%)
Bilateral arm tremor	36 (36%)	not reported
Leg tremor	10 (10%)	12 (6%)
Head tremor	9 (9%)	7 (3.5%)
trunk tremor	7 (7%)	not reported

present in a body part that is not voluntarily activated and is completely supported against gravity) is unusual in patients with MS, and Holmes (or "rubral") tremor is also very uncommon.

In the two main prevalence studies, [6, 74] rest tremor was observed only in the Olmsted County survey (1% of patients), whereas Holmes tremor was observed in neither study. An overview of the affected body parts observed in both studies is given in Table 1. In both studies tremor was most commonly found in the arms. In the London study population, 36% of patients suffered from bilateral arm tremor, making this the most common pattern of limb involvement.

■ Pathophysiology of tremor

The pathophysiology of tremor in MS is a difficult area of investigation, partly because MS is by definition a multifocal disease, so that tremor occurrence cannot easily be linked to a single neuroanatomical site. Systematic postmortem studies on the link between lesion site and the clinical phenomenon of tremor have never been undertaken.

The predominance of action tremors (postural and intention) in patients with MS point to the cerebellum and its connections as the most likely source of tremor production, whereas the rarity of rest tremor argues against an involvement of the basal ganglia. The common occurrence of bilateral tremor might indicate that damage to the cerebellum and its connections is often multifocal.

Another link to the cerebellum in the pathophysiology of tremor in MS is the effect of peripheral cooling on intention tremor. Intention tremor is thought to be modulated through increased long latency stretch reflexes [30]. Cooling has been shown to decrease the sensitivity of muscle spindles [64] and the velocity of peripheral nerve conduction [56]. In two experimental studies, cooling of the arms markedly reduced intention tremor severity in patients with MS [77, 35]. The authors argue that this effect might have been partly due to decreased muscle

spindle function and decreased nerve conduction velocity, which in turn resulted in decreased input into tremor producing cerebellar circuits.

Alusi and coworkers drew attention to the placement site of deep brain stimulation (DBS) electrodes to help understand the neuronal circuits involved in tremor production. They stated that neurosurgeons increasingly chose the nucleus ventralis oralis posterior (VOP) of the thalamus rather than the classic target, the nucleus ventralis intermedius (VIM). This is interesting because the VOP is the basal ganglia output nucleus of the thalamus [6], suggesting that the cerebellar tremors seen in MS might actually be generated by the basal ganglia. The standard electrode placement site reported in the literature, however, is the VIM and no studies comparing placement sites have been published. Whittle and coworkers comment on the difficulty of electrode placement in MS patients: in most patients there are major brain distortions due to demyelination, plaque formation and e vacuo hydrocephalus, and it is therefore uncertain whether the anatomy of these patients conforms to standard stereotactic atlases [100]. Keeping these comments in mind, it seems unwise to base pathophysiological theories purely on DBS electrode placement site.

A range of animal experiments have been undertaken to identify the anatomical structures involved in tremor production (for review [101]). It has been shown that damage or removal of the cerebellar cortex does not induce intention tremor in monkeys, [31, 76] whereas partial or complete cerebellectomy leads to tremor during movement and posture [75, 42, 40]. A slow, 3–5 Hz tremor during target directed movements can also be induced by reversible cooling of the dentate nucleus (the origin of most cerebellar efferents) in monkeys [22].

Most cerebellar efferents project from the dentate nucleus via the superior cerebellar peduncle (brachium conjunctivum) to the red nucleus and the thalamus. According to some studies, transection of the superior cerebellar peduncle causes intention tremor in monkeys [34, 93], whereas other authors do not mention this effect.

Interestingly, Carpenter and colleagues report that tremor induced by transection of the superior cerebellar peduncle can be alleviated by a second lesion in the lateroventral or centromedian thalamus. [19, 20] The results of these animal studies suggest that damage to cerebellar efferents (through lesions of the dentate nucleus or superior cerebellar peduncle) may cause disinhibition of thalamic nuclei which are the main producers of intention tremor.

Although this is an interesting pathophysiologic model of intention tremor production, it remains uncertain whether the results of animal studies can be generalized to patients with MS.

In summary, clinical observation, animal studies and some experimental evidence in humans favour the cerebellum and the thalamic nuclei connected to it as the major locus of intention tremor production, but more research is needed to evaluate the role of the basal ganglia and other systems in tremor production in MS.

■ Assessment of tremor

Depending on the subtype of tremor, several methods for the assessment of tremor severity and its impact on the lives of patients have been developed. Rest tremor is often assessed with the tremor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS). Fahn and colleagues devised the most comprehensive tremor scale for non-parkinsonian tremor in 1984 [33]. This instrument measures tremor in nine body parts at rest, while maintaining a posture and during goal directed movements. It also includes an assessment of arm tremor while writing and pouring water as well as a subscale for functional disability (interference of tremor with dressing, writing, eating etc.). Some studies included in this review use a modified and heavily abbreviated version of this scale, but most studies assess tremor by clinical examination only (e.g. by finger-to-nose testing, drinking from a cup, nine-hole-peg-test or writing and drawing tasks) or use a simple ordinal severity scale, often classifying tremor as absent, mild, moderate or severe. A simple 0–10 tremor severity scale devised by Bain and coworkers [11] has been shown to be a valid and reliable measurement tool in patients with MS [7], but has so far only been used in few clinical studies [6, 4, 15].

Accelerometry and polarized light goniometry are neurophysiologic methods of tremor assessment. While these methods offer an objective measurement of tremor severity, they can only measure one aspect of an often complex movement problem at a time, and e.g. cannot measure the ataxia which often complicates tremor in MS.

Matsumoto and colleagues devised a more complex “quantitative movement analysis technique”, which records the patients' goal directed movements in three dimensions using an electromagnetic tracking device, but the complexity of this method [62] as well as the computer aided tracking tasks employed by Aisen and coworkers [2] prohibit their widespread use.

One of the most important aspects of tremor in MS is its impact on the daily life of the patients. Functional status in MS-patients is often measured by asking the patients to complete questionnaires assessing activities of daily living such as writing, eating or dressing.

Often these scales are self-devised and not validated. Validated scales used in the studies reviewed in this article include the Frenchay Activities Index [85] and the quality of life subscale of the Functional Assessment of Multiple Sclerosis Scale (FAMS) [62].

■ Medical treatment

A summary of the published studies on medical treatment of tremor in MS is given in Table 2. Most of the published literature on medical treatment consists of case reports and uncontrolled open label studies. The few randomized controlled trials comprised small numbers of patients and very likely lacked the power to reveal small treatment effects.

Beneficial effects have been reported for a variety of drugs: case reports and small uncontrolled open label studies claim a positive effect of primidone [47], glutethimide [2], intrathecal baclofen [96] and isoniazid. [80, 32, 67, 38] Controlled clinical trials have been published on the use of propranolol [52], ethanol [52], isoniazid, [52, 44, 16] carbamazepine [86], ondansetron [78] and dolasetron [65].

Koller evaluated the effect of propranolol, isoniazid and ethanol on tremor in three tremulous MS patients in a double blind crossover trial and found no treatment effect for any of the treatments [52]. To the best of our knowledge, no further trials with propranolol have been published, but it is interesting to note that Alusi and coworkers excluded two tremulous MS patients from a thalamotomy trial because they had achieved functional improvement after propranolol use [4].

In an open study the hypnotic-sedative drug glutethimide exhibited visible functional benefit in six of eight MS patients with tremor [2]. Apparently, a controlled trial to confirm these findings was never undertaken.

Two double-blind placebo-controlled trials using isoniazid were published. In the first study reduction of tremor occurred in six of eight patients [16], with functional improvement in four patients. In the second study all six patients had measurable tremor reduction after treatment with isoniazid but this did not lead to functional improvement [44]. Doses of isoniazid used to treat MS-related tremor were very high (up to 1200 mg a day), and treatment was in some patients associated with anorexia and nausea [38] or with a combination of drowsiness, dysphagia and increased bronchial secretion. [32, 67] Other reported side effects were abnormal liver function tests, [80, 32] fatigue [32] and increased weakness [67]. Isoniazid inhibits GABA aminotransferase activity and increases GABA in the central nervous system, but no correlation was found between the degree of GABA elevation in the cerebrospinal fluid and clinical response [16].

Sechi and coworkers published a small single-blind placebo-controlled trial with carbamazepine [86]. They reported improvement of tremor as assessed by clinical examination and accelerometry in all seven included patients, but failed to report whether this translated into functional improvement.

A placebo controlled, double-blind, crossover study, suggested that a single intravenous dose of the 5-HT₃ receptor antagonist ondansetron led to tremor reduction in twelve, and to functional improvement in nine of the sixteen included tremulous MS patients [78]. A subsequent open label study by Gbadamosi and colleagues which used the same intervention found no significant treatment effect [39]. Likewise, a small clinical trial with dolasetron, another 5-HT₃ receptor antagonist, showed no significant treatment effect on cerebellar ataxia [65].

Weiss and coworkers reported a positive effect of intrathecal baclofen in a single patient with bilateral arm tremor [96]. The tremor amplitude decreased almost linearly as the dosage increased and tremor was abolished at a dosage of 250 µg per day. This possible treatment option has, however, not been observed or evaluated in other studies.

In recent years, there has been growing interest in cannabis as a possible therapeutic in MS. In the 1980's a case report [63] and a small uncontrolled study [21] on the beneficial effects of cannabis on tremor and spasticity in MS were published and a survey taken among MS patients revealed that many patients experienced positive effects of smoked cannabis on MS-related symptoms [23].

Baker and colleagues reported a decrease of tremor and spasticity in an animal model of MS after treatment with Δ^9 -tetrahydrocannabinol, the active ingredient of cannabis [12]. All this furthered hopes of cannabis as a possible new treatment option for tremor in MS, but much to the disappointment of tremulous MS patients, several well conducted randomized controlled trials did not show a significant effect of orally administered cannabis extracts [103, 37, 92] or oral Δ^9 -tetrahydrocannabinol [103] on tremor.

■ Surgical treatment

The surgical treatment options for tremor in MS are stereotactic thalamotomy and DBS. An overview of the published studies on surgical treatment is given in Tables 3 and 4. Most of the studies are small observational retrospective studies. When reviewing the literature on surgical treatment, it is surprising as well as disappointing that the majority of studies are remarkably imprecise in providing basic information on the length of follow-up, on adverse effects and-

Table 2 Studies on medical treatment of tremor in MS

Study	n*	study design	intervention(s)	tremor assessment	patients with tremor reduction (%)	patients with improved functional status (%)	adverse effects (n)
Koller, 1984 [52]	3	double-blind placebo-controlled crossover	propranolol (not specified) isoniazid (po.) 1200mg/d ethanol (iv.) 50ml of 10% solution	writing tasks, patient self assessment, clinical examination, accelerometry		no effect	hepatitis while on isoniazid treatment (1)
Sabra et al. 1982 [80]	4	case reports	isoniazid (po.) 400 to 1200mg/d	clinical examination	4 (100%)	4 (100%)	abnormal liver function tests (1)
Duquette et al. 1985 [32]	12	open label	isoniazid (po.) 500–1000mg/d	patient self assessment, clinical examination, blinded evaluation of video tapes	10 (83%)	0	drowsiness, dysphagia, increased bronchial secretions (6) abnormal liver function tests (2) fatigue (2)
Morrow et al. 1985 [67]	5	open label	isoniazid (po.) 700–1200 mg/d	clinical examination	4 (80%)	4 (80%)	increased weakness (2) drowsiness (1)
Francis et al. 1986 [38]	5	open label	isoniazid (po.) 1200 mg/d	clinical examination, polarised light gonioscopy	4 (80%)	0	anorexia and nausea (3)
Hallet et al. 1985 [44]	6	double-blind placebo-controlled crossover	isoniazid (po.) 1200 mg/d	self-rating scales, accelerometry, blinded evaluation of video tapes	6 (100%)	0	None
Bozek et al. 1987 [16]	8	double-blind placebo-controlled crossover	isoniazid (po.) 12 or 20 mg/kg	clinical examination, accelerometry, blinded evaluation of video tapes	6 (75%)	4 (50%)	somnolence (3) **
Sechi et al. 1989 [86]	7	single-blind placebo controlled	carbamazepine (po.) 400 or 600 mg/d	clinical tremor rating scale, accelerometry	7 (100%)	not reported	none reported
Rice et al. 1997 [78]	16	double-blind placebo-controlled crossover	ondansetron (iv.) 8 mg (single dose)	nine-hole peg-test, writing tasks, patient self assessment	12 (75%)	not reported	short-lasting foot dystonia (1)
Gbadamosi et al. 2001 [39]	14	open label	ondansetron (iv.) 8 mg (single dose)	nine-hole peg-test, writing tasks, patient self assessment		no effect	none reported
Aisen et al. 1991 [2]	6	open label	Gluthetimide 750 to 1250 mg	blinded functional assessment by occupational therapist, computer-aided tracking tasks	5 (83%)	5 (83%)	sedation (4)
Clifford, 1983 [21]	8	open label	Δ^9 -THC (po.) 5 to 15 mg	clinical examination	5 (63%)	2 (25%)	none
Zajicek et al. 2003 [103]	365†	double-blind randomized placebo controlled	cannabis extract (po.) Δ^9 -THC (po.)	patient self assessment		no effect	cannabis extract: adverse events in 12 Δ^9 -THC: adverse events in 18 placebo: adverse events in 20
Wade et al. 2004 [92]	13‡	double-blind randomized placebo controlled	cannabis extract (po.)	visual analogue scale symptom reduction		no effect	cannabis extract: \$ 112 adverse events in 80 patients placebo: \$ 53 adverse events in 80 patients
Fox et al. 2004 [37]	14	double-blind randomized placebo controlled crossover	cannabis extract (po.)	tremor rating scale		no effect	cannabis extract: adverse events in 10 placebo: adverse events in 2

THC = tetrahydrocannabinol

* MS patients completing the study

** in this study, one additional patient was withdrawn because of a severe adverse event (dyspnoea, fever, rash, obtundation)

† the main topic of the study is the effect of cannabinoids on spasticity in MS, the patients were asked to assess treatment effect on other symptoms

‡ in this study, patients were asked to name their most troublesome symptom; of the 160 included patients, 13 named tremor

\$ No details are reported on the subgroup of the 13 tremulous patients, the total number of adverse events is reported for the whole groups on active treatment and on placebo (80 patients in each group)

Table 3 Studies on stereotactic surgery for the treatment of tremor in MS

Study	n*	patient characteristics**	lesion site	follow-up	tremor and disability assessment	patients with tremor reduction (%)§	patients with improved functional status (%)§	patients with permanent adverse effects (n)
Cooper, 1960a [25]	2	disabling intention tremor	VL	3 to 12 mo	clinical examination	2 (100%)	not reported	none
Cooper, 1960b [24]	6	disabling intention tremor	unilateral (n = 5) or bilateral (n = 1) VL	Not specifically reported	clinical examination, assessment of filmed tremor	5 (83%)	not reported	increase of contralateral hemiparesis (1)
Krayenbühl et al. 1962 [54]	4	disabling bilateral intention tremor	unilateral (n = 3) or bilateral (n = 1) VL	3 weeks to 6 mo	clinical examination	4 (100%)	4 (100%)	none
Broager and Fog, 1962 [18]	4	severe intention tremor	unilateral VL	1 to 6 mo	clinical examination	4 (100%)	2 (50%)	generalized seizure (1) mental change (1)
Cooper et al. 1967 [26]	32	disabling bilateral intention tremor	unilateral or bilateral VL	12 to 96 mo	clinical examination	27 (85%)	not reported	increase of contralateral hemiparesis (2)
Samra et al. 1970 [81]	25	disabling bilateral arm intention tremor	unilateral or bilateral VL	not specifically reported	clinical examination, assessment of filmed tremor	22 (88%)	not reported	increase of contralateral hemiparesis (1)
Riechert and Richter, 1972 [79]	29	disabling intention (n = 29) and postural (n = 18) tremor	unilateral (n = 28) or bilateral (n = 1) VL	not specifically reported	clinical examination, patient self assessment questionnaires	29 (100%)	“two thirds” of patients	increase of leg paresis (2)
Arsalo et al. 1973 [10]	26	disabling bilateral intention tremor	unilateral VL and subthalamus	3 to 97 mo	clinical examination	21 (80%)	not reported	subdural haematoma (1)
Andrew et al. 1974 [8]	4	disabling postural (n = 2) and intention (n = 4) tremor	unilateral VIM	6 to 36 mo	clinical examination	4 (100%)	not reported	hemiplegia (1)
Van Manen, 1974 [91]	4	severe intention tremor	unilateral VL	3 to 86 mo†	clinical examination	2 (50%)	not reported	not reported separately for MS subgroup
Hauptvogel et al. 1975 [45]	11	severe intention tremor	unilateral (n = 10) or bilateral (n = 1) VL	15 to 86 mo	clinical examination	7 (63%)	4 (36%)	not reported
Mundinger and Kuhn 1982 [68]	84	severe action tremor	ZI, VOP	36 to 120 mo	clinical examination filmed tremor patient self assessment questionnaire	70 (83%)	not reported	not specifically reported
Speelman and van Manen, 1984 [89]	11	severe intention tremor	unilateral VL	3 weeks to 132 mo	clinical tremor and functional rating scales	8 (73%)	0 (0%)	hemiparesis (4) micturition disturbance (2) speech disorder (1)
Kandel and Hondcarian, 1985 [51]	20	severe intention tremor	unilateral (n = 15) or bilateral (n = 5) VL (ZI, FF)	12 to 120 mo	not reported	14 (70%)	not reported	none
Hitchcock et al. 1987 [48]	30	tremor	Thalamus	24 mo	clinical examination functional rating scales	50%	25%	not reported
Wester et al. 1990 [97]	9	severe intention tremor	unilateral VOA and VOP	3 to 89 mo mean: 24 mo†	questionnaire sent to treating neurologist	6 (66%)	6 (66%)	hemiparesis (5) mental changes (3) dysphasia (3) dysarthria (2) subdural haematoma (1)
Goldman et al. 1992 [43]	2	severe intention tremor unresponsive to medication	unilateral VL	3 mo 34 mo	clinical tremor rating scale	2 (100%)	0 (0%)	dysarthria (1)
Whittle and Haddow, 1995 [98]	9	severe rest, kinetic, postural or intention tremor	unilateral VL	12 mo	clinical examination and evaluation of video tapes	9 (100%)	2 (22%)	depression (2)

Table 3 Continued

Study	n* patient characteristics**	lesion site	follow-up	tremor and disability assessment	patients with tremor reduction (%)§	patients with improved functional status (%)§	patients with permanent adverse effects (n)
Shahzadi et al. 1995 [87]	33 severe tremor	unilateral VIM	3 to 120 mo	clinical examination ability to drink from a waterfilled cup	22 (67%)	17 (51%)	not reported
Hooper and Whittle, 1998 [50]	6 severe postural (n = 4) or intention tremor (n = 2)	unilateral VL	14 to 73 mo mean: 51 mo	Barthel Index	1 (16%)	1 (16%)	not reported
Critchley and Richardson, 1998 [27]	24 disabling intention tremor	unilateral (n = 22) or bilateral (n = 2) VIM	mean: 26 mo	clinical tremor and functional rating scales	18 (75%)	2 (8%)	hemiparesis (1) seizure (2) MS relapse (3) dysarthria (1)
Schuurman et al. 2000 [85]	5 severe arm tremor	unilateral VIM‡	6 mo	clinical tremor and functional rating scales	5 (100%)	0 (0%)	severe gait or balance disturbance (2)
Niranjan et al. 2000 [72]***	3 severe action tremor	unilateral VIM	2 to 11 mo median 6 mo†	clinical tremor rating scale, patient self assessment of functional improvement	3 (100%)	3 (100%)	none
Alusi et al. 2001 [4]	11 severe postural and intention tremor	unilateral VOP (n = 7), ZI (n = 3), STN (n = 1)	12 mo	clinical tremor and functional rating scales	11 (100%)	7 (64%)	depression (3) seizures (2) hemiparesis (1) dysphasia (1)
Matsumoto et al. 2001 [62]	6 severe tremor	unilateral VIM	3 to 12 mo	clinical tremor and functional rating scales, novel movement analysis tool	6 (100%)	0 (0%)	MS relapse (2)
Bittar et al. 2005 [15]	10 disabling postural and intention arm tremor	unilateral VOP (distal tremor), unilateral ZI (proximal tremor) or unilateral VOP and ZI (mixed tremor)	12 to 50 mo: mean 16 mo	clinical tremor rating scale	not individually reported, overall improvement of mean tremor scores: postural: 78% intention: 72%	not reported	hemiparesis (3) seizures (1)

VOP = nucleus ventralis oralis posterior; VOA = nucleus ventralis oralis anterior; VIM = nucleus ventralis intermedius; ZI = zona incerta; VL = nucleus ventralis lateralis; STN = nucleus subthalamicus; FF = Forel's Field

* MS patients with completed surgical intervention and remaining in the study until end of follow up

** an effort is made to distinguish between predominance of intention or postural tremor although many terms to describe tremor subtypes are used in the studies

*** In this study, gamma-knife radiosurgery is used

§ improvement as described in case reports or measured at the end of follow-up on any scale used in the study

† in this study, MS patients were grouped together with patients with other movement disorders, no details are given for the MS-subgroup

‡ thalamotomy was followed six months later by contralateral DBS electrode implantation in patients with bilateral tremor

most importantly-on the effect on functional status and tremor associated disability.

The first study on thalamotomy for tremor in MS was published by Cooper in 1960 [25]. Brice and colleagues were the first to report improvement of tremor through continuous thalamic DBS in 1980 [17].

■ Strategies for patient and treatment site selection

The earlier studies on thalamotomy used the thalamic nucleus ventralis lateralis (VL) as the target, whereas the nucleus VIM was chosen in most DBS studies and

most later thalamotomy studies. This preference for the VIM is probably due to the experience with this thalamic nucleus in the treatment of tremor in Parkinson's disease (PD) and essential tremor (ET). Research groups in Oxford and London used the nucleus VOP and the zona incerta (ZI) as targets for both lesional surgery and DBS, but the results yielded with these targets [4, 69, 15] were not different from those reported for VIM or VL thalamotomy or stimulation.

The same researchers advocate the use of tremor frequency analysis during movement tasks as a method to identify patients likely to benefit from surgery [60]. This may be a valuable tool for patient selection, although it has only been validated in a

Table 4 Studies on DBS for the treatment of tremor in MS

Study	N*	patient characteristics	stimulation site	follow-up	tremor and disability assessment	patients with tremor reduction (%)§	patients with improved functional status (%)§	patients with permanent adverse effects (n)
Brice and McLellan, 1980 [17]	2	severe bilateral arm intention tremor	bilateral subthalamic	5 mo 6 mo	clinical examination	2 (100%)	2 (100%)	**
Nguyen and De-gos, 1993 [71]	1	severe unilateral distal postural arm tremor	unilateral VIM	17 mo	clinical tremor and functional rating scales	1 (100%)	1 (100%)	not reported
Siegfried and Lippitz, 1994 [88]	9	severe intention tremor	unilateral (n = 8) or bilateral (n = 1) VIM	not reported	not reported	9 (100%)	not reported	not reported
Benabid et al. 1996 [13]	4	severe arm tremor†	VIM†	≥ 6 mo	clinical tremor rating scale	0 (0%)‡	no detailed report†	intracerebral haemorrhage (1)
Geny et al. 1996 [41]	13	severe postural tremor (n = 12), moderate intention tremor (n = 1)	unilateral VIM	8 to 26 mo mean: 13 mo	clinical tremor and functional rating scales	9 (69%)	12 (92%)	MS relapse (3)
Whittle et al. 1998 [99]***	5	severe arm tremor	VL	not reported	not reported	not reported	not reported	not reported
Hay, 1999 [46]	1	head and limb tremor	unilateral thalamus	2 mo	not reported	1 (100%)	not reported	not reported
Montgomery et al, 1999 [66]	14	disabling arm tremor	unilateral VIM	variable	clinical tremor rating scale	15 (100%)	not reported	MS relapse (1)#
Schulder et al. 1999 [83]	5	severe bilateral postural and intention arm tremor	unilateral VIM	>6 mo	clinical tremor rating scale, patient self assessment of functional improvement	5 (100%)	3 (60%)	Ms relapse (2)
Taha et al. 1999 [90]	2	bilateral limb, head or voice tremor†	bilateral VIM (bilateral DBS or unilateral DBS plus contralateral thalamotomy)	mean: 10 mo	clinical tremor rating scale	2 (100%)	not reported	not reported separately for MS subgroup†
Schuurman et al. 2000 [85]	5	severe arm tremor	unilateral or bilateral VIM	6 mo	clinical tremor and functional rating scales	3–5 (60–100%)§	0 (0%)	dysarthria (2) severe gait or balance disturbance (1) arm ataxia (1) not reported separately for MS subgroup†
Krauss et al. 2001 [53] Loher et al. 2003 [61]§§	2	severe tremor	unilateral or bilateral VIM†	3 to 24 mo, mean: 12 mo†	clinical tremor rating scales, assessment of video tapes	2 (100%)	not reported	not reported separately for MS subgroup†
Matsumoto et al. 2001 [62]	3	severe tremor	unilateral VIM	3 to 12 mo	clinical tremor and functional rating scales, novel movement analysis tool	3 (100%)	0 (0%)	none
Hooper et al. 2002 [49]	10	disabling arm tremor	unilateral thalamus	12 mo	clinical tremor and functional rating scales	10 (100%)	0 (0%)	intracerebral haemorrhage (2) generalized seizure (2) increased dystonic posturing of left foot impairing ambulation (1)
Nandi et al. 2002 [70]	1	severe bilateral postural and intention tremor	unilateral ZI	12 mo	clinical examination	1 (100%)	1 (100%)	wound infection (2)
Berk et al. 2002 [14]	12	disabling arm tremor	unilateral VIM	12 mo	clinical tremor and functional rating scales, patient self assessment questionnaire	significant tremor reduction, not individually reported	no significant improvement	not reported
Wishart et al. 2003 [102]	4	bilateral arm tremor	bilateral VL	15 to 31 mo	clinical tremor rating scale	4 (100%)	4 (100%)	MS relapse (1) dysarthria (1)

Table 4 Continued

Study	N*	patient characteristics	stimulation site	follow-up	tremor and disability assessment	patients with tremor reduction (%)§	patients with improved functional status (%)§	patients with permanent adverse effects (n)
Schulder et al. 2003 [84]	9	disabling arm tremor	unilateral thalamus	9 to 48 mo,	clinical tremor and functional rating scales, patient self assessment	8 (88%)	3 (33%)	MS relapse (3)
Nandi et al. 2004 [69]	10	disabling arm tremor	unilateral (n = 6) or bilateral (n = 4) VOP and ZI	3 to 23 mo	computer-aided tracking tasks	significant tremor reduction, not individually reported	not reported	seizure (1) dysarthria (1) wound infection (1)
Bittar et al. 2005 [15]y	10	disabling postural and intention arm tremor	unilateral VOP (distal tremor), unilateral ZI (proximal tremor) or unilateral VOP and ZI (mixed tremor)	3 to 23 mo:	clinical tremor rating scale	not individually reported, overall improvement of mean tremor scores: postural: 64% intention: 36%	not reported	monoparesis (1)

VIM = nucleus ventralis intermedius; ZI = zona incerta; VL = nucleus ventralis lateralis

* MS patients with completed surgical intervention and remaining in the study until the end of follow up

§ improvement as described in case reports or measured at the end of follow-up on any scale used in the study

** in this study two patients had complete surgery and in three, surgery was aborted. A worsening of dysarthria is reported in one patient, it is unclear whether this patients had completed surgery

*** This study mostly discusses difficulties in target localisation and patient selection

in this study, one patient did not complete surgery due to an intraoperative VIM haemorrhage

† in this study, MS patients were grouped together with patients with other movement disorders, no details are given for the MS-subgroup

‡ For the whole group, tremor was "inconsistently, less significantly [than tremor of Parkinson's Disease and essential tremor] or not improved. If improvement was achieved it lasted only a few months"

§ The exact number of patients with improved tremor cannot be ascertained the way the data is presented in this study

§§ Both studies are on one patient cohort, the relevant data on MS patients are derived from both studies

small number of patients and studies in which this technique is used [4, 69, 15] do not report better results than studies without this selection method.

The site for lesional surgery or electrode placement is classically chosen relative to the site of the anterior and posterior commissures using a standardized atlas. More recently, surgeons tried to refine this placement strategy with microelectrode recording within the target area. Neurons discharging synchronous to peripheral tremor are identified and the treatment site is placed in an area where the most tremor related neuronal activity is found. [73, 59, 57, 58]

This method of treatment site selection is often used in studies on tremulous patients with PD and ET, but only a small number of MS-patients were included in these studies. [87, 13, 66, 62, 84] Since this method offers a theoretical advantage over the classical methods of treatment site selection, it should be further evaluated.

■ Outcome after surgical treatment

Because of the many shortcomings of the published studies, the results need to be interpreted with great

caution. It does, however, seem as if almost all patients experience tremor reduction immediately after thalamotomy, and roughly 70% of patients continue to benefit from thalamotomy beyond a follow-up period of one year (Table 3). In the three studies on thalamic DBS with a follow-up period longer than one year, 69% to 100% of the patients experienced reduced tremor [41, 84, 102]. Functional improvement after both thalamotomy and DBS is much more variable and unfortunately not reported in many studies (Tables 3 and 4).

Niranjan published an interesting study on gamma-knife thalamotomy as a possible alternative to neurosurgery. In this study all three patients with MS-related tremor experienced marked improvement of tremor after radiosurgery. Unfortunately, no further studies have been published to evaluate this interesting non-invasive treatment option [72].

There are two trials in which thalamotomy and DBS were compared in patients with MS. In a randomized controlled trial conducted by Schuurman and colleagues [85] patients with ET, tremor due to PD and tremulous MS patients were randomized to undergo either VIM thalamotomy or DBS. Five tremulous MS patients were randomized to each

group. After a short follow-up period of six months, there were no significant differences between thalamotomy and DBS in functional outcome for the MS subgroup. In the same study, fewer adverse effects were observed in the DBS group, except for the subgroup of MS patients, where adverse effects were about equal for both interventions (Tables 3 and 4). Bittar and colleagues compared cumulative tremor scores for intention and postural tremor between patients undergoing VOP/ZI thalamotomy or DBS in a non-randomized study [15]. Ten patients were in each group. Interestingly, after a mean follow-up period of 15 to 16 months, patients in the thalamotomy group had a better outcome (tremor reduction: 78% for postural tremor and 72% for intention tremor) than patients in the DBS group (tremor reduction: 64% for postural tremor and 36% for intention tremor). However, as there were more adverse effects in the thalamotomy group, no clear recommendations could be given.

Adverse events reported for the neurosurgical interventions comprised increase of hemiparesis, dysarthria, dysphasia, mental changes, depression, seizures, intracerebral haemorrhage, subdural haematoma, wound infection and MS relapse. Thalamotomy was associated with a higher risk of adverse events than DBS. Bilateral thalamotomy carries such a high risk of adverse effects, that it is no longer recommended. If bilateral treatment is necessary, either bilateral DBS or unilateral thalamotomy followed by contralateral DBS are possible treatment options.

■ Other treatment options

Electromagnetic fields, limb cooling, physiotherapy, weight bracelets, orthoses and specialized software have been advocated as additional treatment options.

Sandyk and Dann reported a reduction of intention as well as postural tremor in three tremulous MS patients treated with pulsed electromagnetic fields [82], but these interesting findings have not been substantiated in a larger trial.

Albrecht and coworkers published a small clinical trial on the effect of arm cooling on intention tremor [3]. In their study, patients achieved significantly better results on a clinical testing battery after immersion of the tremulous arm in ice water. As this effect lasted for about 45 minutes the authors recommend limb cooling to achieve transient tremor

control for activities such as working with a PC, signing a document or self-catherisation. In a similar study, Feys and colleagues report tremor reduction lasting for about 30 minutes after limb cooling with a special cooling device [35].

Weighted wrist cuffs are a mechanical tool to reduce tremor amplitude, and one article reported their beneficial effects in three MS patients [28]. Although wearing bracelets decrease tremor amplitude and therefore may offer some benefit to tremulous patients, their effect on intention tremor is small and their use is therefore unlikely to yield important functional improvement. A more advanced computer aided tremor reducing orthosis provided functional benefit in a small case series including patients with MS [1].

Physiotherapy aimed at improving ataxia in MS was evaluated by Armutlu and coworkers. In their small pilot study they found that rehabilitative physiotherapy using Johnstone pressure splints was superior to physiotherapy alone [9]. Unfortunately no larger trials followed this pilot study, so that it remains uncertain which patients may benefit from which form of physiotherapy.

The use of a mouse driven computer system is a special challenge for tremulous MS patients. Feys and colleagues published a study on the use of specialized software developed to aid computer use in 36 tremulous MS patients and found significant improvement in the time needed to complete some basic mouse driven computer operations [36].

Conclusion

The treatment of tremor remains a great challenge for everyone caring for patients with MS. Drug treatment with currently available medication is unsuccessful in most cases and much more research on the pathophysiology and biochemistry of tremor production in MS will be necessary before an efficient medical treatment can be developed. Stereotactic surgery can be an effective means to treat severe tremor, but it is currently uncertain whether lesional surgery or DBS is the treatment of choice. Larger clinical trials comparing both interventions are needed. Other treatment options, including physiotherapy, tremor reducing orthoses, and limb cooling can lead to valuable improvements in activities of daily living.

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