RESEARCH ARTICLE

Indications and approaches for functional neurosurgery in multiple sclerosis, including the role for lesional surgery and deep brain stimulation

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Abstract

Multiple sclerosis is a chronic and disabling condition of the central nervous system, associated with variable and wide-ranging symptoms. In some patients, functional neurosurgery may be considered for the relief of symptoms including tremor and pain. This could include lesional surgery or deep brain stimulation. In this review we evaluate the evidence for lesional neurosurgery and deep brain stimulation in multiple sclerosis, comparing these approaches and associated outcomes, and identifying the key symptoms which are thought to be amenable to intervention.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease, targeting the axons and myelin sheaths of white matter, and cortical and deep grey matter of the central nervous system, resulting in brain, spinal cord and optic nerve lesions. The condition affects over 2 million people worldwide, with a female predominance, usually starting in the third or fourth decade of life. It is currently incurable, and tends to have a step-wise course with episodes of neurologic symptoms, which may resolve partially or completely. Neurologic symptoms may be a result of slowed or blocked conduction due to demyelination, while inflammatory mediators such as cytokines may also play a role in inhibiting neuronal function [1]. Treatments focus on delaying disease progression and ameliorating symptoms, with intensive research to identify a potential cure. Current disease modifying treatments include immunomodulatory strategies [1]. Clinical symptoms include optic neuritis, cerebellar symptoms such as diplopia and ataxia, along with limb weakness, urinary incontinence and cognitive decline [2]. The ultimate aim in MS research is to be able to re-myelinate areas of the central nervous system (CNS) that have become demyelinated, or to prevent demyelination occurring in the first place.

Stereotactic surgery, including lesional surgery and deep brain stimulation (DBS), has a role in the management of multiple sclerosis for alleviation of cerebellar outflow tremors. Other stereotactic interventions to reduce symptom severity and improve quality of life of symptoms in MS as spasticity, pain, gait dysfunction, and pelvic organ dysfunction have been considered as targets for functional neurosurgery. In this paper we will compare DBS and thalamotomy as interventions for tremor, and also consider whether the options of DBS or lesional surgery are relevant for other areas of symptom control in MS.

Stereotactic vs. functional surgery for MS tremor

MS movement disorder can include proximal postural instability, dysmetria, and tremor [3]. Tremor affects 25-60% of patients with MS and may be disabling, interfering with basic daily activities including feeding, dressing, writing and working [4,5]. Achieving good tremor control could potentially reduce disability and improve quality of life. The tremor in MS is often complex; there may be proximal and distal components, combined with postural, action and intention components [6,7]. It is thought that tremor occurs as a result of inflammation and damage along cerebello-thalamocortical pathways resulting in impaired afferent feedback from muscle spindle afferents via the cerebellum and thalamus to the motor cortex [4]. Pharmacological treatments for MS tremor include botulinum toxin, and isoniazid which have shown some benefit in tremor alleviation [8 9 10]. However, for patients with pharmacologically refractory, severe, disabling tremor, surgical strategies may be considered.

Interrupting the communication between thalamus and cortex, either via a thalamic lesion or DBS can block the onset of the tremor by preventing the aberrant information reaching the motor cortex [11]. However, it is not clear whether effective

DBS is a result of stimulation of thalamocortical projection neurons or subthalamic tracts that influence cerebello-thalamic afferents[6]. Imaging studies have found an association between lesion load in brainstem and severity of tremor [12], and physiologically, tremor cells have been described in the thalamus, whose oscillatory patterns match the electromyogram (EMG) tremor potentials [7]. Various assessment scales exist to quantify tremor; these include the Tremor Rating Scale and the Tolosa-Fahn-Marin Tremor Rating Scale, and functional outcome scales commonly used include the Expanded Disability Status Scale (EDSS), Incapacity Status Scale (ISS) and Environmental Status Scale (ESS) [5].

Lesional surgery

Lesional surgery, in the form of stereotactic thalamotomy, predates DBS for MS tremor. Thalamotomy for MS tremor was arguably first described in the literature by Cooper in 1960, with a series of 12 patients which included 6 with MS [13]. Lesions work by silencing aberrant neuronal firing within cerebello-thalamocortical pathways, and although lesional surgery became less popular after DBS was introduced, it is now being considered again for certain settings where DBS might not be possible, with newer minimally invasive alternatives such as gamma knife and focussed ultrasound as options under exploration for patients who may not be suitable for an invasive DBS or lesional procedure.

The thalamotomy studies spanned a period from 1960 to 2019. Earliest studies employed chemoablative techniques, whereas later techniques tended to report the use of radiofrequency lesions. The majority of studies were retrospective case series. In all studies, more than 50% of patients had an improvement in contralateral tremor following thalamotomy and in some papers, improvement was seen in closer to 75% or more [11,14,15].

In Cooper's 1967 retrospective series, there was a marked improvement or complete abolishment of tremor in 27 out of 32 patients (85%)[11,14,15]. Speelman & Van Manen (1984) [15] reported good effects for tremor in their series (8 out of 11 had improvement in intention tremor) but also reported disease progression and serious side effects including 4 patients who had a permanent hemiparesis and 1 patient who died 3 weeks post-operatively of an aspiration pneumonia. Critchley et al. 1998 described results from a series of 24 patients and 29 lesional procedures for MS tremor. There was immediate improvement in 23 procedures (79%) and sustained improvement in 18 (62%) with 13 complications. Fatigue was described as a side effect in 7 patients [16].

In a case control series, in which 13 patients underwent surgery and 11 matched controls (no surgery) were studied, Alusi et al. (2001) described significant improvements in upper limb postural and kinetic tremor, spiral scores and head tremor at 3 months and 12 months after lesional surgery, compared with the group who did not undergo surgery[17]. The lesion group also had better tremor-related disability scores. The optimal target was thought to be the subthalamic area. In general, however, improvements in quality of life did not seem to always correlate with the size improvement in tremor severity, as described by Whittle et al. 1995, [18] underlining the fact that MS is a multi-disabling disease and that improvements

in a single domain (tremor) may not translate to real gains in quality of life. Although some studies suggested that lesional surgery could promote disease progression in MS [15,19], Alusi et al compared disease progression between patients undergoing lesional surgery and matched controls, and did not see a significant difference between the groups in terms of changes in Barthel ADSS Index or EDSS [17].

Overall the rate of adverse events following lesional surgery for MS reported in the literature is high. According to Bittar et al, early complications were as high as 60% following thalamotomy, with 30% of patients experiencing permanent complications[20]. Adverse events described in the literature include death, bulbar problems, hemiparesis, seizures, and MS progression [11,15,16]. In the earlier studies, worsening of bulbar function and subsequent aspiration may have been linked to the adverse events [21].

Mathieu et al. 2007 describe gamma knife thalamotomy as alternative option to radiofrequency ablation[22]. 6 patients underwent the procedure, all of whom had improvement in tremor, and 4 of whom had functional benefit. There were no major complications- one patient had a contralateral hemiparesis which resolved with corticosteroids. Focussed ultrasound thalamotomy is a non-invasive technique which uses multiple converging ultrasound beams to produce a thermal ablation within the thalamus. This technique was initially described for the treatment of essential tremor and parkinsonian tremor [23,24] , but has been described at a case report level for MS tremor [25]. The group describe a high degree of tremor suppression (up to 80% at one year) but there were long-term side effects, including dysarthria, which took 1 year to fully resolve. There was a degree of perilesional oedema, which needed to be controlled with corticosteroids, and it was not clear how objectively the extent and consequences oedema can be anticipated and managed.

Deep brain stimulation

The first description of DBS for tremor in MS was by Brice and McLellan in 1980 [26], and since then, around 20 clinical series or studies have been reported, summarized in recent reviews by Koch et al (2007) [27] and Brandmeir et al. (2019) [28]. Traditional DBS targets for MS tremor include the ventral intermediate nucleus of the thalamus (VIM), and/or ventral oralis posterior nucleus of the thalamus (VOP) contralateral to the side of the tremor. The zona incerta (ZI) and subthalamic nucleus (STN) were more recently described; the ZI particularly for proximal action tremor. Contralateral VIM and VOP are also the targets considered in thalamotomy. Traditionally, outcomes with DBS have been seen to be mixed for MS tremor[29]. Brandmeir et al. 2019 published a meta-analysis of published literature to investigate the effect of DBS on MS tremor [28]. 13 studies were identified suitable for meta-analysis. A random effects meta-analysis model was carried out, providing level III evidence that at 12 months, DBS produced an improvement in the Hedges mean tremor score by 2.86 ($p<0.00001$), with a rate of adverse events of between 8 and 50%. Targets included within this study were VIM alone (7 studies), VIM and VO (2 studies), ZI or VO and ZI (3 studies) and VC (1 study).

Berk et al (2002) [30] found that there was an overall improvement in tremor score and both postural and action components

of the tremor when assessed at 2 and 12 months post surgery. However, on evaluating quality of life measures at the same time points, there were no significant improvement on SF-36 measures, which the authors suggest may have been related to unrealistic expectations about what the procedure would achieve. Zakaria et al. (2013) [31] found that in 16 patients there was a significant reduction in tremor, with 11/16 achieving at least 30% tremor reduction. There were statistically significant improvement in subscores on the Fahn scores for feeding, but other quality of life measures did not reach significance although there was a trend towards improved quality of life in the patients with improved tremor. In a study of 13 patients with MS tremor, Geny et al. (1996) [32] found that there was marked improvement in proximal tremor (improvement in 9/13 cases) but that change in distal tremor was less pronounced. They also found that functional improvement was more variable than tremor improvement and suggested that interplay with other factors such as additional neurological disability might be occurring [32]. However, in this cohort, almost all patients reported an improvement in fatigue associated with activities of daily living after the tremor control with DBS. Torres et al. described results for 10 patients, undergoing Vim DBS, finding that 50% of patients reported benefit following DBS, but only 30% had more than 50% tremor reduction at 1 year. Thevathasan et al, 2010 [33] described a 44% improvement in Total Clinical Rating Score with stimulation and reported that tremor reduction could occur in limbs where strength was conserved, responding to the view that the phenomenon of permanent tremor reduction following DBS could be a result of weakness rather than true tremor suppression [34]. In some studies which included multiple tremor aetiologies, patients with tremor related to MS appeared to be less responsive to DBS than those with other aetiologies [35,36].

In terms of exploration of other targets, Plaha et al, 2008 describe a 57.2% improvement in tremor score with bilateral caudal ZI stimulation [37] , and Herzog et al. 2007, in their series of 21 patients undergoing thalamic DBS for tremor of various aetiologies, suggested that the most effective contacts were located in the subthalamic area rather than the thalamus itself [6]. A recent single blinded study of dual lead thalamic stimulation (VO and VIM) showed promise, with response to stimulation in 8/12 patients and significant reduction in mean Tolosa-Fahn-Marin Tremor Rating Scale scores following DBS [38].

Direct comparison between lesions and stimulation

Papers directly comparing DBS with lesional surgery are few. Altinel et al. 2019 [39] , carried out in a meta-analysis to compare the two techniques. They included 15 randomized studies across essential tremor, Parkinson's disease (PD) and multiple sclerosis. There were 4 studies directly comparing DBS with lesional surgery, 4 studies comparing lesions with control, and 7 studies comparing DBS with control. They found no significant difference between DBS and lesional surgery in terms of tremor control, quality of life, cognitive or neuropsychiatric outcomes, however, the majority of included studies had patients with exclusively PD or essential tremor (ET) tremor, with only one paper including patients with MS tremor. This paper, by Shuurman et al (2008) [40], which randomised patients either to

thalamotomy or thalamic DBS followed up 68 patients, of whom 10 had MS (5 in the lesion group and 5 in the DBS group) stated that although there was no statistically significant difference in tremor scores between the groups, functional outcome, as measured by the Frenchay Activities Index, was better for patients with DBS than thalamotomy, and also that DBS led to quality of life gains above those achieved in the lesion group. Adverse events were seen more frequently in the thalamotomy group, although interestingly, this difference was more marked for the PD patients included in the study than those with MS. Furthermore, it should be noted that the only death due to surgery occurred in the DBS rather than the lesional group, highlighting the possibility of severe adverse effects of both techniques. Bittar et al (2005) [20], on the other hand, found in a prospective study that thalamotomy produced significantly greater improvements in postural tremor and intention tremor at follow up than DBS (postural tremor: 78% reduction in thalamotomy group compared with 64% reduction in DBS group; intention tremor: 72% reduction in the thalamotomy group compared with 36% for DBS). In this study, VOP was targeted for distal action tremor and ZI for proximal action tremor in both groups. The rate of permanent neurological deficits was higher in the lesion group than the DBS group (3/10 for the thalamotomy group compared with 1/10 for the DBS group).

Lesional surgery or DBS?

The obvious difficulty in comparisons between the techniques is that there have been major advances in technology between the period of time that lesions were employed and the current DBS era, which enable more accurate localisation of the target area. These include significant developments in MRI technology, which allows segmentation of the thalamus for accurate localisation [41,42], as well as post-operative care. Non-surgical treatments for MS have also evolved significantly since the first lesion papers, which may influence factors such as disease progression following surgery. Furthermore, the emphasis on outcome scores has become more prominent since the original lesion papers and as a result the outcomes from later series (lesion or DBS) tend to be evaluated in a way that can be more easily objectified. Combined with this, there are few studies which directly compare lesions with DBS, thus the question of whether DBS is superior to thalamotomy for MS tremor has not been clearly answered.

The main advantages of lesional surgery are that it can be done at a lower cost [43], with no permanently implanted devices, reducing long-term infection risk and the need for ongoing follow-up and engagement with the neurosurgical team. These factors suggest advantages of the technique for patients in low and middle income countries where DBS remains costly and inconvenient. The drawbacks, however, are its irreversibility and the related risk of permament side effects, particularly in patients with bilateral tremor, since bilateral thalamotomy is generally avoided due to high morbidity and mortality associated with irreversible complications should they occur [32 44]. Furthermore, in a neurodegenerative disease such as MS, there is expectation that disease progression may result in development of further tremor despite the lesion at longer follow up intervals. In patients with DBS, this may be handled by altering the intensity or distribution of

electrical stimulation; following a lesion there is no modification option available.

Other roles for DBS and lesional surgery in MS

Pain

Pain in MS can be multifactorial and of either neuropathic or non-neuropathic origin [45]. Purely neuropathic pain is thought to occur in about 5% of MS sufferers at 4 years following MS diagnosis, while "pain of any type" occurs in about 36% of patients [46]. Pain is sometimes related to fatigue and depression, but can also be linked more directly with MS lesions, as described in the case of whole body pain secondary to a lesion within the parietal operculum [47] and a thoracic demyelinating lesion in a child which resulted in symptoms of acute abdominal pain, possibly through preventing transmission of autonomic efferent activity resulting in abdominal dysmobility [48]. In many cases pain related to MS lesions responds to pharmacological treatment, such as methylprednisolone.

Chronic pain was one of the earliest indications for DBS [49 50 51] and may be an underexplored therapeutic option for patients with chronic intractable neuropathic pain in MS. Traditional DBS targets for chronic pain include the ventral posterior lateral and ventral posterior medial thalamic nuclei (VPL/VPM) [52] [49] [53] and the periventricular/periaqueductal grey area [50] [53]. Other targets described in the literature include the posterior hypothalamus [54] and the anterior cingulate cortex [55].

Trigeminal neuralgia is one of the more common causes of chronic neuropathic pain in MS, and has recently been shown to occur at a 15 fold higher rate in MS patients than general neurology patients (Laakso et al. 2020). Although in some MS cases it is caused by vascular compression of the trigeminal nerve [56] it has been linked in a retrospective study to demyelinative lesions in the region of the trigeminal ganglion (Laakso et al. 2020) [57]. Posterior hypothalamus DBS for trigeminal neuralgia in five patients MS has been described by Cordella et al (2009) [54]. All patients had prior inadequate responses to balloon decompression surgery, and all reported pain amelioration following DBS; one patient had complete pain relief and the others had residual pain that could be controlled pharmacologically.

Pelvic organ symptoms

Pelvic organ symptoms including urinary and and sexual dysfunction can develop in multiple sclerosis. Lower urinary tract symptoms arising from neurogenic lower urinary tract dysfunction occurs in up to 75% of MS patients [58 59]. Features include detrusor overactivity, detrusor underactivity and detrusor-sphincter dyssynergia [59], and can produce a combination of voiding dysfunction and incontinence with impact on quality of life and increased morbidity associated with urinary tract infections. Research studies based primarily on patients with movement disorders have shown that DBS can modulate bladder sensation and voiding parameters, including increasing maximal bladder capacity in the case of PAG [60] and STN [61] DBS. Standard globus pallidus interna (GPi) DBS at stimulation parameters appropriate for movement disorder symptom control (in a dystonia cohort) reduced maximal flow rate and increased post void residual, as well as eliminating detrusor overactivity

contractions [62]. In theory this could be harnessed to aid MS patients with symptoms related to detrusor overactivity; furthermore as GPi neuromodulation clearly appears to have an important role in voiding [62-64] stimulation parameters could be explored to identify other possible effects of GPi DBS that might be relevant to voiding dysfunction in MS and optimised by altering the pattern of stimulation.

Disease progression

Studies of functional neurosurgery for tremor raised interesting questions about the role of DBS and lesions in disease progression. Some studies found that patients appeared to experience MS relapse or disease progression following DBS or thalamotomy [16,38,65]. A post-mortem study also found that DBS was also associated with plaque formation close to the electrode, which fortuitously resulted in permanent tremor suppression [66]. More work could be done to investigate the effect of electrical stimulation or lesion formation on the MS disease process at a molecular level, particularly as DBS systems are becoming MRI compatible.

Conversely, electrical stimulation is being tested as an interventional option to promote myelination in a trial registered in 2019, investigating transorbital electrical stimulation of the optic nerve as a possible remyelinative strategy in optic neuritis (https://clinicaltrials.gov/ct2/show/NCT04042363). This is based on evidence that moderate, repetitive neuronal activity driven by optogenetic stimulation can improve remyelination and restoration of conduction in mice with LPC-induced demyelination within the corpus callosum [67]. This raises the possibility that deep brain stimulation, at the correct stimulation parameters, could be neuro-protective or restorative in the context of MS lesions. At present, however, there is currently no evidence from human studies that electrical stimulation promotes remyelination in MS (although electrical stimulation shown to promote peripheral nerve regeneration [68].

Conclusion

There is still great need to capitalise on the opportunities for functional and stereotactic neurosurgery in the treatment of MS. Both thalamotomy and DBS have good effect on tremor reduction, although it remains to be understood why quality of life measures lag behind tremor scores in terms of improvement following surgery. Alternative indications for DBS, including pain, bladder function and possibly disease modification, are areas for future exploration.

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