Deep brain stimulation for cluster headache

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Abstract
Cluster headache is a severely debilitating disorder that can remain unrelieved by current pharmacotherapy. Alongside ablative neurosurgical procedures, neuromodulatory treatments of deep brain stimulation (DBS) and occipital nerve simulation have emerged in the last few years as effective treatments for medically refractory cluster headaches. Pioneers in the field have sought to publish guidelines for neurosurgical interventions focusing upon DBS and occipital nerve stimulation, and discuss the indications for and mechanisms of DBS including translational insights from functional neuroimaging, diffusion weighted tractography, magnetoencephalography and invasive neurophysiology.

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1. Introduction

Cluster headache (CH) is an excruciating primary headache syndrome. Originally described in 1926 by Wilfred Harris and Bayard Horton, it was likened to “a knife being driven in through a point between the outer canthus of the eye and the hair line”. The extreme nature of the pain and recurrent course of the syndrome was noted then by Horton in the suicidal intent of his patients: “Their pain was so severe that several of them had to be constantly watched for fear of suicide. Most of them were willing to submit to any operation which might bring relief”. Today many cases are still refractory to the best medical management and for these patients neurosurgical intervention may be appropriate.

CH is defined by strictly unilateral pain lasting between 15 minutes and three hours, occurring at least once every other day and up to eight times a day. The episodes are associated with nausea, restlessness and ipsilateral cranial autonomic symptoms commonly including conjunctival injection, lacrimation, rhinorrhea, ptosis and eyelid swelling. Prevalence estimates vary between 0.05% and 0.3%. About 80% to 90% of patients are affected episodically, with headache periods that last usually two weeks to three months separated by at least one month of remission, often with striking seasonality. The remainder of patients suffer chronic CH with attacks lasting more than one year and remissions of less than one month or not at all.

A proportion of patients suffer medically intractable headaches defined variously by failure to respond to conventional pharmacotherapy and disease duration. Numerous ablative surgical interventions have been performed in these patients; a testament to their desperate position. Such procedures include Gasserian ganglion glycerol injection, trigeminal ganglion or pterygopalatine ganglion radiofrequency ablation, gamma knife radiosurgery, and microscopic surgical sectioning of the trigeminal nerve, and nervus intermedius. Such techniques report variable success. Their efficacy is difficult to interpret due to limited long-term follow-up and uncontrolled studies in a relapsing and remitting condition. Common complications include treatment failure, anesthesia dolorosa, corneal damage, contralateral recurrence and death. Consequently, non-ablative neuromodulatory treatments have been undertaken recently with some success.

2. Safety and efficacy

Deep brain stimulation (DBS) is a well-accepted, safe and efficacious alternative to ablative surgery with an estimated 30,000 to 40,000 Parkinson’s disease patients treated worldwide. Improvements in our understanding of brain function coupled with technological advances are expanding its clinical indications.
Neuroimaging of CH has localised abnormalities to the ipsilateral posterior inferior hypothalamic grey matter.\(^{18}\) This led to the first use of DBS in the condition in a patient in whom further lesional surgery was contraindicated.\(^{19}\) We have summarised outcomes of subsequent case series to August 2008 (Table 1). Exceptional results have been achieved by Italian investigators in Milan, the first centre to use the technique.\(^{20}\) They have published the largest detailed series of 16 patients implanted, with 61% pain free and no reported significant side effects. A Belgian centre reported four patients successfully implanted with two pain free and one substantially improved.\(^{21}\) Of eight patients implanted in California, five demonstrated a greater than 50% reduction in headache intensity or frequency by at least one year of follow-up; however, none have been reported as pain free.\(^{22,23}\) Most recently a multi-centre series of six patients implanted in Germany reports three patients almost pain free and three treatment failures.\(^{24}\) Additional presented abstracts not published in detail and unpublished cases are reported elsewhere.\(^{20}\)

In Oxford, UK, we recently treated three patients, all of whom are pain free with no side effects with follow-up varying from 6 months to 2 years.\(^{25,26}\) A further two patients have since been treated. The coordinates we use are 6 mm posterior, 2 mm lateral, and 8 mm inferior to the mid-commissural point (Fig. 1), as described in the original functional MRI (fMRI) study showing hypothalamic activation in CH.\(^{18}\) The first two patients in Milan, and the Belgium cohort were stimulated at similar deep brain targets but subsequent series have used 3 mm posterior to the mid-commissural point, 2 mm lateral to the midline and 5 mm inferior to the comissural plane, as revised by the Milan group in 2003.\(^{27}\) As yet there is no discernible difference in efficacy although the Belgian group proposed that it might explain more severe oculomotor disturbances in their patients and the higher voltages required to obtain efficacy.\(^{21}\) However, we have not found these side-effects in our Oxford patients.

Significant reported side effects include a fatal case of intracerebral haemorrhage,\(^{21}\) one implantation failure due to an intraoperative panic attack,\(^{21}\) and one intraoperative transient ischaemic attack.\(^{23}\) Three case series, including our own, reported no significant complications,\(^{20,24}\) although an asymptomatic intraventricular haemorrhage was noted in a single patient in the Milan series.\(^{20}\) Transient mild side-effects are universal at stimulation amplitudes above 1.5 V, or during rapid changes in amplitude, including vertigo, transient diplopia and dysphoria in two cases.\(^{20,21,23,24}\) In the short term there is concern over a potentially greater risk of catastrophic intracerebral haemorrhage, compared with the risk in DBS for other indications due to the depth and location of the brain targets. In the long-term, ablation of the posterior hypothalamus might be expected to cause temperature dysregulation, autonomic dysfunction, altered sleep and mood. Studies in stimulated patients have demonstrated sympathetic overactivity,\(^{28}\) but no effect on temperature regulation or hormone levels and improved sleep duration and quality related to reduced nocturnal attacks.\(^{29}\) This may be explained by the location of the electrode tip posterior to the mammillo-thalamic tract, believed by some to represent anterior periaqueductal grey rather than posterior hypothalamus.\(^{32}\)

In general, outcomes are variable but clearly the procedure can be startlingly effective. Three out of five studies have operated on 6 to 8 patients and reported a 50% or greater success rate, defined as either pain free or having a greater than 50% improvement in frequency or intensity of headaches. The Milanese group stands out as having treated the most patients with a large proportion of patients with neither pain nor significant side-effects at a mean follow-up of four years post-procedure. Such results may be explained partly by greater experience with the technique. With 100% of three patients pain-free in Oxford so far, greater proportions of pain-free patients across centres may be achieved as clinical experience increases.
Additional multi-centre trials will clarify the applicability of the technique in different patient populations with different surgical teams. Randomised, double-blind, controlled trials are ideal but challenging to perform in neurosurgery. Chronic CH can remit spontaneously in up to 30% of patients, while placebo effects can lead to improvements in up to 40% of patients. One group reports 9 of 12 chronic CH patients going into remission while on a waiting list for DBS. N-of-1 trials with patients as their own controls have been carried out for stimulation in Parkinson’s disease, chronic pain and obsessive–compulsive disorder, and are predicated upon blinded assessment during randomised periods of minutes to months where the stimulator is either on or off. Hurdles to such trials include patient concordance and ensuring that the patient remains truly blinded to device status. Furthermore, the often reported period of months for onset and loss of efficacy with stimulation in CH would require long randomisation periods. The field awaits the results of such a trial recently commenced with 12 CH implantations by Lanteri-Minet and co-workers.

3. Indications

A multi-centre consensus group published proposals for patient selection in DBS for CH in 2004. Appropriate candidates should have chronic unilateral CH, for at least two years, with daily attacks. Their headaches should be refractory to best medical treatment and there should be no medical, psychological or ethical contraindications. Further recommendations on what constitutes “intractable” or “refractory” headache have refined what might be considered as failure of an adequate trial of medical therapy.

Consensus guidelines are important for invasive procedures with potentially devastating side effects. However, they should also be flexible in a new technique where published data are available on fewer than 50 patients. The decision to intervene should always be taken on an individual assessment of the risks and benefits to the patient, based on personal experience and available evidence. For example, although current experience and guidelines are limited to chronic CH, episodic sufferers might benefit from the technique. In the original study 8 of 17 patients who demonstrated hypothalamic involvement in CH suffered episodic CH.

In DBS for Parkinson’s disease, studies of outcome and patient selection criteria make use of global rating scales such as the Unified Parkinson’s Disease Rating Scale (UPDRS). Such scores take into account functional disability and quality of life, which are notably absent from outcome studies and patient selection criteria for DBS in CH. Other CH studies have used the Migraine Disability Assessment Score (MIDAS), Short Form-36 (SF-36) and the
Beck Depression Inventory (BDI)\textsuperscript{41} to demonstrate severely impaired quality of life in CH sufferers. Use of such quantitative measures in reporting outcomes of DBS for CH would facilitate a broader consideration of which patients will benefit most from intervention.

More generally, detailed analyses of pre-operative and post-operative patient characteristics may reveal subgroups that fare better or worse than others, enabling intervention to be tailored more appropriately. Positron emission tomography (PET)\textsuperscript{18,42} and morphometric MRI\textsuperscript{43} studies show hypothalamic abnormalities in CH averaged over several patients that might be best explored initially on an individual basis. Application of such techniques in a clinical context may facilitate individual patient selection, as is done in neurosurgery for epilepsy.

4. Cost effectiveness

Cost effectiveness analyses of DBS are limited to Parkinson’s disease, demonstrating a reduced need for medications and care.\textsuperscript{44,45} For DBS in general, British National Health Service tariffs cost clinical assessment at about £20,000, surgery at £21,000 and stimulation equipment at £12,000 per patient, with implantable pulse generator changes needed about every five years as an ongoing cost.\textsuperscript{17} A stereotactic frame and computer planning station cost £150,000 with a three-year lifespan. In CH, this is to be compared with medication costs of sumatriptan subcutaneous injections, three injections per week at £3,450 per year, oxygen at £520 per year and topiramate, 200 mg per day at £625 per year for prophylaxis, which over one decade of chronic CH adds up to £46,000. Thus, year-on-year savings from DBS are likely to be considerable, particularly because the mean patient age is 45 years for those treated thus far, assuming that the therapeutic effect of stimulation is sustained. Considering indirect cost benefits also, the Milan group reported all but 1 of 16 patients returning to work after stimulation.\textsuperscript{20}

5. Mechanisms

5.1. Functional neuroimaging and diffusion weighted tractography

The severe unilateral pain of CH corresponds to activation of the ophthalmic division of the trigeminal nerve while the autonomic symptoms are consistent with parasympathetic outflow carried by the facial nerve.\textsuperscript{46} Centrally, the seasonal and diurnal pattern of CH has long hinted at a hypothalamic circadian pacemaker.\textsuperscript{47} In addition, clinical studies have demonstrated disruption of the normal circadian cycle of hypophysial hormone release in CH, particularly melatonin and cortisol.\textsuperscript{46,49} More recently, PET demonstrated ipsilateral posterior inferior hypothalamic grey matter activation during CH attacks.\textsuperscript{18,42} and morphometric MRI shows increased neural density in the same area in CH sufferers in remission.\textsuperscript{43} These findings led to the tentative conclusion that the so-called “cluster generator” may be located here. Hence, high frequency stimulation was postulated to functionally ablate this generator.\textsuperscript{19}

The observation that a beneficial effect typically develops over weeks of continuous stimulation rather than days suggests, however, that the truth may be more complicated.\textsuperscript{50} Diffusion weighted tractography seeded from the electrode site in a CH patient shows pathways to the medial lemniscus, ipsilateral frontotemporal orbital cortex, reticular nucleus, superior cerebellar peduncle, cerebral cortex and angular gyrus in the controls studied.\textsuperscript{25} A PET study of ten CH patients with hypothalamic DBS showed that stimulation increased uptake in the ipsilateral hypothalamus, thalamus, somatosensory cortex, precentral, anterior cingulate cortex and trigeminal nucleus and ganglion.\textsuperscript{51} Decreased uptake was observed in the middle temporal gyrus, inferior temporal gyrus bilaterally, posterior cingulate cortex and contralateral anterior insula. Both activated and deactivated areas are implicated in the higher pain matrix in acute CH, suggesting that posterior hypothalamic stimulation functionally modulates these higher pain circuits, as opposed to pure inhibition of a hypothalamic pacemaker. Activation of the ipsilateral trigeminal nucleus and ganglion suggest additional modulation of the trigeminal nucleus caudalis, and hence the brainstem trigeminothalamic reflex, rather than local inhibition of these structures. Indeed there is no clinical evidence for trigeminal nucleus inhibition.\textsuperscript{21} This reflex is implicated in basal vessel vasodilatation, demonstrated in PET studies of CH patients.\textsuperscript{52} Key areas of the descending anti-nociceptive pathway were not activated, which argues against a purely anti-nociceptive mode of action.

The PET study\textsuperscript{52} investigated immediate changes in activation only, whereas the therapeutic effect usually takes weeks to months. Its authors suggest that the observed changes might result in long-term disruption of a hypothalamic “clock-pulse generator”,\textsuperscript{53} which in turn modulates autonomic and trigeminovascular areas. This might imply that the cluster generator itself lies elsewhere, perhaps in the limbic system since clusters are often associated with affective stimuli.\textsuperscript{54} Modulation of the orexinergic system may be the effector of a hypothalamic gating mechanism. Orexins might be underexpressed in CH and other primary headache syndromes, which potentially could respond to orexin agonists.\textsuperscript{55} Studies in animals have shown that the orexinergic system modulates nociceptive processing,\textsuperscript{56} and is intimately linked anatomically with the posterior hypothalamus.\textsuperscript{57} Administration of orexins is anti-nociceptive,\textsuperscript{58} modulates dual inputs to the trigeminal nucleus caudalis,\textsuperscript{59} and inhibits dorsal vasodilatation in mice and rats.\textsuperscript{60} The system is also implicated in the regulation of autonomic and neuroendocrine functions.\textsuperscript{61}

5.2. Invasive neurophysiology

Translational studies of mechanisms of the effect of DBS in CH continue on several fronts. In Oxford we recently recorded the first observation of local field potentials (LFPs) from the posterior hypothalamic during an episode of CH.\textsuperscript{26} During the attack there was a prominent peak in local field potential spectra between 16 Hz and 22 Hz, with increased activation observed between 16 Hz and 30 Hz for the most superficial contacts and 16 Hz to 40 Hz in the mid contacts. This finding provides new insight into the activity of the posterior hypothalamus during an attack. The identification of a specific neural rhythm during CH attacks provides the first direct support for hypothalamic involvement in CH, which has long been suspected from clinical results and less direct functional neuroimaging methods.\textsuperscript{16,50} The presence of a frequency-localised power modulation appears to identify the first potential triggering mechanism in CH.

Analysis and reproduction of the spectra may enable CH induction through stimulation for study purposes, and uncover the role of the hypothalamus at different stages of a cluster episode. Ongoing translational studies seek to combine LFP recording with autonomic testing of patients to delineate the autonomic and nociceptive mechanisms in the hypothalamic relay circuits that underlie CH.\textsuperscript{24} Further understanding of LFPs and their relationship to attacks might facilitate understanding of treatment failures and help optimise patient selection and stimulation concomitant with the potential development of “smart”, demand-driven stimulators, responsive to and activated by CH attacks.
5.3. Magnetoencephalography

We have used magnetoencephalography (MEG) in the study of DBS for pain,20,22 and are now investigating its application to the study of DBS in CH. MEG is a non-invasive modality that enables whole-brain activation changes to be discretely mapped with potentially similar spatial resolution to fMRI yet superior temporal resolution, and without the safety concerns associated with MRI use in patients with DBS. Although DBS has been investigated at low frequencies, we have recently validated its use at 130 Hz to 180 Hz in a CH patient.64 Preliminary study of the patient demonstrated activation in the periaqueductal grey region only when the stimulator was turned off, perhaps implicating concomitant activation of the two structures in a “cluster generator” matrix. Further studies may complement invasive neurophysiology in elucidating temporal relationships between the deep brain structures from which causality might be inferred, and a neural model of CH pathogenesis and DBS action proposed.

6. Occipital nerve stimulation: A neuromodulatory alternative

Occipital nerve stimulation (ONS) has emerged as a less invasive neuromodulatory alternative to DBS for chronic CH. Recent case series show modest efficacy with minimal side effects in 19 patients treated to date.65–67 Direct comparison of some results with DBS is difficult as pre-operative attack frequencies were almost weekly rather than daily.65 ONS has not yet achieved as high proportions of pain-free patients as DBS, and current series suggest it is more commonly associated with complications requiring surgical revision. However, to date there are no reports of catastrophic complications with ONS. Thus, several centres now offer the less invasive treatment first.20,22 For meaningful comparison, more series with similar baseline patient characteristics and multi-centre trials to compare both treatments are desirable.

7. Conclusions

DBS for CH has already had a huge impact on the lives of those people who are now pain free and able to return to work. Further study is needed to consolidate treatment efficacy through blinded trials, as the placebo effect in CH is potentially significant. Ideally these should be multi-centre since data from a large single centre case series requires replication elsewhere. Multi-centre trials also facilitate consensus regarding indications for intervention. Parallel study of ONS will help to clarify the place of each technique in the armamentarium of therapies for CH.

Neuroimaging techniques and invasive neurophysiology are rapidly advancing understanding of the pathophysiology and mechanisms of CH. Such advances have therapeutic implications, not only in refining the technique of DBS, but also other neurosurgical and pharmaceutical therapies where new anatomical and pharmacological targets may be developed. Together these translational research and clinical studies offer hope to many CH sufferers previously only able to consider relatively ineffective ablative brain surgery as a last resort.

Competing interests

None declared.

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References