

Ventral tegmental area deep brain stimulation for refractory chronic cluster headache



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ABSTRACT

Objective: To present outcomes in a cohort of medically intractable chronic cluster headache (CCH) patients treated with ventral tegmental area (VTA) deep brain stimulation (DBS).

Methods: In an uncontrolled open-label prospective study, 21 patients (17 male; mean age 52 years) with medically refractory CCH were selected for ipsilateral VTA-DBS by a specialist multidisciplinary team including a headache neurologist and functional neurosurgeon. Patients had also failed or were denied access to occipital nerve stimulation within the UK National Health Service. The primary endpoint was improvement in the headache frequency. Secondary outcomes included other headache scores (severity, duration, headache load), medication use, disability and affective scores, quality of life (QoL) measures, and adverse events.

Results: Median follow-up was 18 months (range 4–60 months). At the final follow-up point, there was 60% improvement in headache frequency ($p = 0.007$) and 30% improvement in headache severity ($p = 0.001$). The headache load (a composite score encompassing frequency, severity, and duration of attacks) improved by 68% ($p = 0.002$). Total monthly triptan intake of the group dropped by 57% posttreatment. Significant improvement was observed in a number of QoL, disability, and mood scales. Side effects included diplopia, which resolved in 2 patients following stimulation adjustment, and persisted in 1 patient with a history of ipsilateral trochlear nerve palsy. There were no other serious adverse events.

Conclusions: This study supports that VTA-DBS may be a safe and effective therapy for refractory CCH patients who failed conventional treatments.

Classification of evidence: This study provides Class IV evidence that VTA-DBS decreases headache frequency, severity, and headache load in patients with medically intractable chronic cluster headaches. *Neurology*® 2016;86:1676–1682

GLOSSARY

CCH = chronic cluster headache; **CESG** = Clinical Effectiveness Supervisory Committee; **CH** = cluster headache; **DBS** = deep brain stimulation; **HAL** = headache load; **HIT-6** = Headache Impact Test-6; **IPG** = implantable pulse generator; **MIDAS** = Migraine Disability Assessment Scale; **NHS** = National Health Service; **ONS** = occipital nerve stimulation; **PCS** = physical component summary; **QoL** = quality of life; **SF-36** = Short Form-36; **TAC** = trigeminal autonomic cephalalgia; **VRS** = verbal rating scale; **VTA** = ventral tegmental area.

Cluster headache (CH) is a trigeminal autonomic cephalalgia (TAC)¹ characterized by attacks of severe, strictly unilateral cranial pain associated with ipsilateral cranial autonomic features.^{2,3} CH has a prevalence of 0.1%–0.2% and chronic CH (CCH) occurs in 10%–15% of patients whose attacks occur for more than 1 year without remission, or with remissions lasting less than 1 month.^{4–8}

Standard medical therapy comprises acute and prophylactic treatments, which are usually effective.⁹ However, in a small but significant number of highly disabled individuals, attacks are intractable. For these patients, peripheral (occipital nerve stimulation [ONS] or sphenopalatine ganglion stimulation) and central neuromodulation (ventral tegmental area [VTA] deep brain stimulation [DBS]) have been carried out with promising results.^{10–15}

Supplemental data at Neurology.org

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We investigated the efficacy of VTA-DBS when used as a humanitarian intervention in patients who had exhausted every other option available to them within the framework of the UK National Health Service (NHS). We present a prospective study of 21 consecutive patients with CCH, treated using a MRI-guided and MRI-verified approach to VTA-DBS, focusing on changes in headache characteristics, quality of life (QoL), disability, and mood.

METHODS Standard protocol approvals, registrations, and patient consents. The UK National Institute for Health and Care Excellence published guidance concerning DBS for intractable TACs in March 2011 (<https://www.nice.org.uk/guidance/ipg381/chapter/1-Guidance>), advising arrangements for clinical governance, consent, audit, and research. In keeping with this, and under the supervision of our institution's Clinical Effectiveness Supervisory Committee (CESG), we offered VTA-DBS to CCH patients who had failed ONS or in whom NHS funding for ONS had been declined. The procedure was provided on the basis of a humanitarian intervention. Patients were provided with CESG-approved patient information booklets and gave written consent.

Patient selection. Included patients fulfilled the International Classification of Headache Disorders–II diagnostic criteria for CCH¹ and had experienced highly disabling, medically refractory symptoms for at least 2 years. CCH was classified as medically intractable if patients failed adequate trials of at least 5 of the following 7 drugs: verapamil, lithium, methysergide, topiramate, melatonin, gabapentin, and valproate. A failed trial was defined as an unsatisfactory response, side effects intolerance, or contraindication to the agent's use.¹⁶ All patients were considered for ONS prior to DBS and had either been refused funding or had failed to respond adequately. Sphenopalatine ganglion stimulation was not available in the United Kingdom during the study period. Referrals were made by a single tertiary specialist headache clinic to a DBS multidisciplinary team at the same center. Neuropsychological evaluations and MRI brain scans were performed to rule out cognitive impairment, brain lesions, or significant brain atrophy.

Outcome measures and follow-up. Outcome data were collected and recorded prospectively and included headache

frequency, headache severity, headache load, disability scores, affective scores, QoL measures, adverse events (including surgical complications, stimulation-induced adverse events, and morbidity), and reduction in preventive and acute treatment.

Headache severity was measured on the verbal rating scale (VRS) for pain (0 being no pain and 10 being the worst pain imaginable). Patients reported the mean headache intensity during individual attacks. The individual scores were then averaged over the observation period. Headache frequency was defined as the number of CH attacks per day. Headache load (HAL) was defined as \sum (severity [on the verbal rating scale] \times duration [in hours]) of all headache attacks occurring over a 2-week period. These measures were assessed using headache diaries collected preoperatively (baseline), at commencement of DBS therapy, and at 3, 6, and 12 months and yearly thereafter. Patients with multiple headache types kept separate diaries for CH attacks and other headache syndromes; headache parameters were calculated for each headache type.

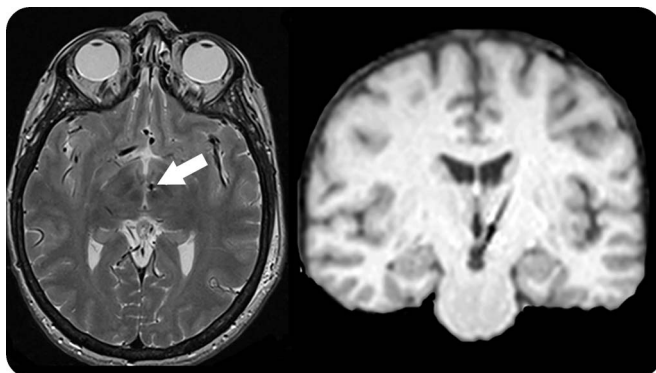
Responders were defined as patients with sustained HAL reduction $\geq 30\%$ since this was deemed meaningful in line with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines.¹⁷

Disability measures, QoL, and affective scores were collected using questionnaires. The Short Form-36 (SF-36) measuring both the physical component summary (PCS) and mental component summary scores was used to assess health-related QoL at baseline and after stable improvements in responders, or after a year of continuous stimulation in nonresponders.¹⁸ Since specific tools for measuring the disability of CH have not yet been validated, disability was assessed using the Migraine Disability Assessment Scale (MIDAS)¹⁹ and the Headache Impact Test–6 (HIT-6).²⁰ MIDAS and HIT-6 have been used extensively to assess primary headache disorders. They have previously been used to assess the disability of CH and hemicrania continua patients treated with ONS.^{21,22} The Hospital Anxiety and Depression Scale–anxiety and Hospital Anxiety and Depression Scale–depression²³ were used to evaluate the presence and degree of anxiety and depression before and after surgery. Other questionnaires included the Beck Depression Inventory II and the EuroQoL (EQ-5D).

Surgical procedure. DBS leads were implanted using a stereotactic MRI-guided and MRI-verified approach without microelectrode recording as detailed in previous publications (Leksell frame model G; Elekta Instrument AB, Stockholm, Sweden).^{24,25} The first 11 patients had lead implantation performed under local anesthesia; in the remaining 10 patients, leads were implanted under general anaesthesia.²⁴ The anatomical target was the ipsilateral VTA. The location for the deepest contact of the 3389 Medtronic lead was defined on a 1.5T T2-weighted axial stereotactic MRI at a level immediately above the mammillary bodies, anteromedial to the hypointense red nucleus and posterolateral to the hypointense mammillothalamic tract. Immediately after lead implant, location was verified with a stereotactic MRI scan (figure 1) in patients without ONS. Postoperative stereotactic CT scan was performed in patients with implanted ONS hardware. The lead was then connected to a single or dual channel implantable pulse generator (IPG) (Medtronic, Minneapolis, MN) implanted in the infraclavicular region on the same day of lead implantation or within a week, as a staged procedure under general anesthesia.

DBS programming. In the weeks following surgery, open label programming was conducted to define optimal stimulation parameters. Six patients (29%) had a delay of 1–3 months before

Figure 1 Immediate postoperative stereotactic MRI demonstrates the deep brain stimulation lead in the left ventral tegmental area



their stimulation was started. This was because they reported a clear stun effect period postoperatively, during which attacks improved without any stimulation. In these patients, DBS was not initiated until they reported a return to baseline in terms of attack frequency. All devices were programmed with a frequency of 185 Hz and a pulse width of 60 μ s.¹¹ Voltages were adjusted according to self-limiting side effects (diplopia, vertigo, oscillopsia, and ophthalmoplegia) in single or multiple steps, depending on the patient. Stimulation parameters were kept constant for the first 3 months and were adjusted after this if patients were not responding.

Statistical analysis. IBM SPSS Statistics package v22 was used for all the statistical analyses.

Percentage change from baseline was used where appropriate. The data at baseline were assessed for normality using Kolmogorov-Smirnov test and by inspecting the Q-Q plot and frequency distribution histogram prior to determining appropriate statistical tests. Whenever the distribution was not normal, nonparametric tests were used and the median was given instead of the mean. Wilcoxon signed-rank test was used to compare treatment effect at each timepoint from baseline. To adjust for multiple comparisons when present, Bonferroni corrections were applied by multiplying each test-statistics *p* value by the number of comparisons. There were 4 comparisons in the HAL case (for separate tests between baseline and 3, 6, and 12 months, and last follow-up), and 2 for QoL and disability scores (for separate tests between baseline and 6 and 12 months). Statistical significance was set at 5%. Raw and normalized data were tested and descriptive statistics were reported where applicable.

Research questions. When carried out in patients with refractory CCH:

1. Does VTA-DBS improve headache frequency, severity, and headache load? (Class IV evidence)
2. Does VTA-DBS improve disability, mood, and QoL? (Class IV evidence)
3. Is VTA-DBS safe? (Class IV evidence)

RESULTS Patient sample. Between April 2009 and November 2013, 21 patients (17 male) with a mean (SD) age of 52 (10) years underwent VTA-DBS for CCH. CCH was the sole headache diagnosis in 16 patients (76%). Other primary headaches were present in the remaining 5 patients (24%), including episodic migraine, sporadic hemiplegic migraine, and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing. The mean (SD) time from CH onset until surgery was 15 (7) years. The mean (SD) time from CH onset until the last follow-up point was 18 (8) years. Sixteen patients received unilateral DBS electrode implantation (8 left) for strictly unilateral cluster CH; the remaining 5 patients (24%) underwent bilateral DBS electrode implantation for side-variable CH attacks. Six (29%) patients had prior ONS implanted with limited or short lasting effect with a median time of 4 years prior to undergoing DBS. Of these, 3 patients had the ONS removed before undergoing DBS surgery (table e-1 on the *Neurology*[®] Web site at Neurology.org).

Comorbidities in this patient group included depression (*n* = 10), previous suicide attempts or ideation (*n* = 4), cancer (*n* = 3), other chronic headache syndromes (*n* = 5), epilepsy (*n* = 3), Parkinson disease (*n* = 1), chronic fatigue syndrome (*n* = 1), stroke (*n* = 1), heart disease (*n* = 1), hereditary spastic paraparesis (*n* = 1), and temporomandibular joint dysfunction (*n* = 1). Four patients were smokers and 3 were ex-smokers.

Implanted leads were within a mean (SD) of 0.8 (0.4) mm from the planned target. Postoperatively, 3 patients complained of intermittent diplopia, which resolved in 2 patients following stimulation parameters adjustment and persisted in the other patient who had a previous history of ipsilateral trochlear nerve palsy following a head injury; this diplopia persisted even when stimulation was switched off. One patient developed a keloid scar over the IPG incision. A superficial wound infection developed in 1 patient, which resolved with antibiotics treatment. There was no surgical mortality or other significant morbidity. Postoperative follow-up ranged from 4 months to 5 years with 19 patients having at least 1 year of follow-up.

Frequency and severity of headache attacks (VRS). At the final follow-up point, there was a 60% overall improvement in the median headache frequency from 5 to 2 attacks per day (*p* = 0.007). The percentage of patients who had at least 30% and 50% reduction in median frequency of attacks was 62% and 52%, respectively.

The overall improvement in median headache severity was 30%, from 10 to 7 points on the VRS (*p* = 0.001). The percentage of patients who had at least 30% and 50% reduction in median headache severity on the VRS was 43% and 24%, respectively, at the final follow-up point (table e-2 shows effect of DBS on CH attack frequency, severity, and duration at last follow-up).

Headache load. Eleven patients (52%) showed a maximum reduction in the HAL of more than 80% during the follow-up period. Within 3 months of surgery, the median change in HAL was 62%, at 6 months it was 59%, and at 12 months it was 79% (table 1 and figure 2, A and B).

The percentage of patients who had at least 30% and 50% reduction in headache load was 81% and 76%, respectively, at the final follow-up point.

Four patients (19%) failed to respond to treatment (<30 reduction in HAL). Three of these had also failed to respond to ONS treatment previously.

The subset of patients with prior ONS (*n* = 6) had a failure rate of 50% (*n* = 3). There was no change in the median HAL at 3 months, deterioration of 3% at 6 months, and deterioration of 23% at

Table 1 Median headache load

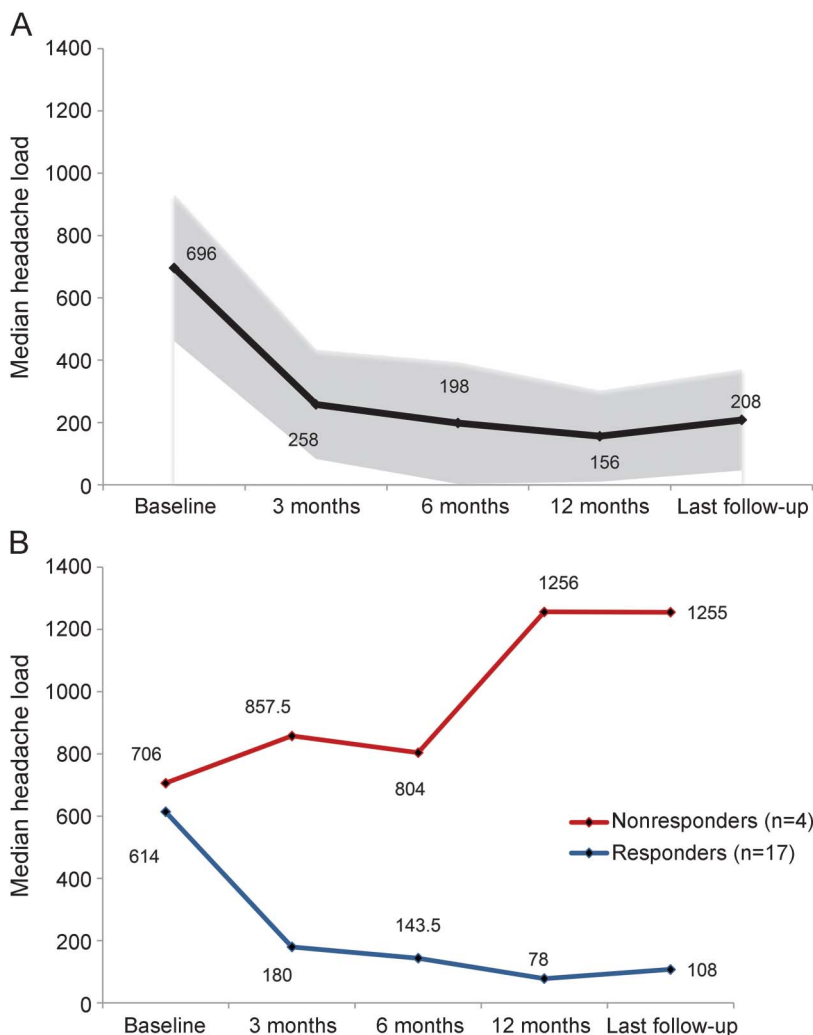
	Baseline	3 mo	6 mo	12 mo	Last follow-up
Median	696	258 (n = 17, p = 0.002)	198 (n = 16, p = 0.01)	156 (n = 20, p = 0.003)	208 (n = 21, p = 0.002)
Median absolute deviation	235	175	155.5	146	162
Median improvement, %		62	59	79	68

Median headache load at baseline and at postoperative follow-up points with percentage of improvement in headache load relative to baseline. The *p* values are Bonferroni-corrected; they represent individual tests at each time point relative to baseline (number of comparisons = 4).

12 months (n = 6). In this subgroup, the 3 patients who improved had a modest but meaningful reduction of the median HAL of 34%, 30%, and 34% at 3, 6, and 12 months, respectively.

Reduction in acute and preventive treatment. Seven patients were on preventive medications prior to DBS insertion. Six continued to take preventive medications after surgery although 4 of these reduced the dose of a medication and 3 stopped at least

1 medication. One patient increased the dose of verapamil as it had an improved effect on preventing attacks post-DBS. Eleven patients were taking triptans prior to treatment and 12 were using oxygen. At the last follow-up point, 7 patients were using triptans and 11 were using oxygen. One patient started to use triptans again posttreatment as it was found to be effective whereas previously it had not. The total monthly triptan intake of the whole group was 873 doses pretreatment and 376 doses posttreatment, a reduction of 57% (table e-3).

Figure 2 Median headache load (HAL) evolution

(A) Median HAL at baseline and over the course of follow-up with a median absolute deviation error band. (B) Median HAL of responders and nonresponders.

QoL, mood, and disability measures. Median improvement in HIT-6 was 4 points (corrected *p* = 0.018) at 6 months and 6 points (corrected *p* = 0.034) at 12 months. The PCS section of the SF-36 scores showed an improvement of 13% (corrected *p* = 0.038) at 6 months (table 2 and figure 3).

DISCUSSION This open-label prospective study suggests that MRI-guided and MRI-verified DBS of the VTA is a safe and effective procedure in patients with CCH whose symptoms are refractory to other treatments. Symptomatic improvement was sustained over time and was accompanied by significant improvements in a number of QoL scales.

In 1998, a PET study reported increased activation in the posterior hypothalamic region during CH attacks, though the maximal activation was centered over the VTA.^{26,27} This led to the first DBS procedure in 2001, with attacks disappearing within 48 hours of starting stimulation.¹⁰ This pioneering group referred to the anatomical target as the posterior hypothalamus rather than the VTA, and went on to report the first series of 5 patients in 2003 and 19 patients in 2013.^{11,28} To date, different centers have published data on over 70 patients with DBS for medically intractable CCH with varying response rate but an overall good safety record with the exception of one fatal intracerebral hemorrhage during a microelectrode-guided procedure.^{12-14,28,29}

A randomized controlled crossover trial of DBS for CCH did not show any significant difference between sham and active stimulation during the blinded crossover period. However, 1-year outcome revealed that 6/11 patients had >50% reduction in

Table 2 Quality of life, disability, and mood

	Baseline			6 mo				12 mo			
	Median	MAD	No.	Median	MAD	No.	p Value	Median	MAD	No.	p Value
MIDAS	137	74	18	100	91	18	0.16	29	29	17	0.08
HIT-6	69	4	19	65	5	19	0.02 ^a	64	8	16	0.03 ^a
HAD-A ^b	(11)	(5)	19	(9)	(5)	19	0.22	(9)	(5)	17	0.5
HAD-D ^b	(12)	(6)	19	(10)	(6)	19	0.22	(10)	(5)	17	0.32
BDI-II	28	11	18	25	12	18	0.27	20	8	15	0.47
SF-36 PCS	32	6	14	36	9	14	0.04 ^a	35	6	13	0.27
SF-36 MCS	32	9	14	36	12	14	1.10	34	16	15	1.94
Euro-QoL	0.65	0.09	11	0.68	0.07	11	1.25	0.71	0.07	10	0.08
Euro-Scale	49	19	11	55	15	11	0.28	45	17	10	1.89

Abbreviations: BDI-II = Beck Depression Inventory II; HAD-A = Hospital Anxiety and Depression Scale-anxiety; HAD-D = Hospital Anxiety and Depression Scale-depression; HIT-6 = Headache Impact Test-6; MAD = median absolute deviation; MIDAS = Migraine Disability Assessment Score; SF36-MCS = Short Form-36 mental summary score; SF36-PCS = Short Form-36 physical summary score.

Quality of life, disability, and mood data at baseline and 3, 6, and 12 months postsurgical follow-up. The *p* values are Bonferroni-corrected; they represent individual tests at each time point relative to baseline (number of comparisons = 2).

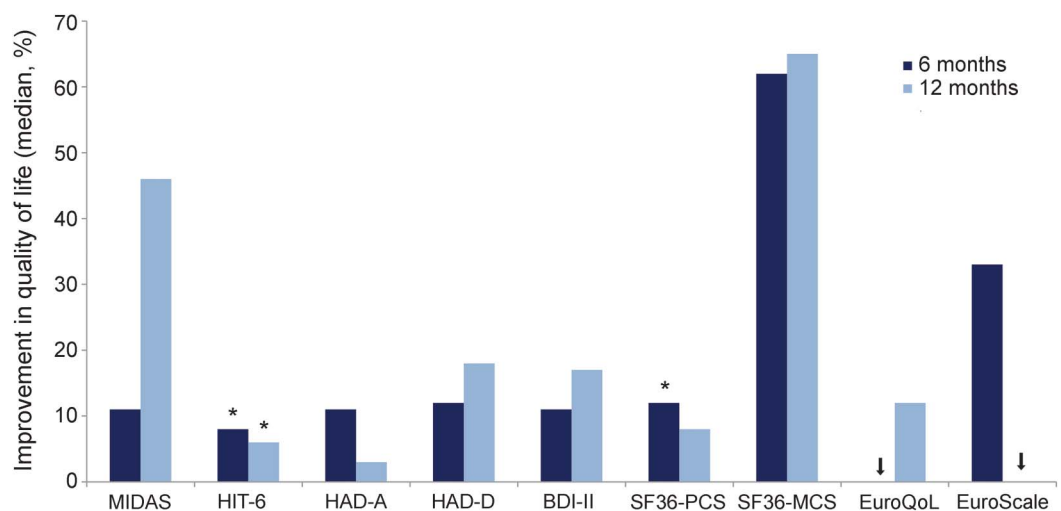
^a*p* Value ≤ 0.05.

^bNormally distributed data presented in mean and SD instead of median and MAD.

attack frequency and 3 patients were pain-free. The difference in outcome may be explained by the short 1-month crossover period within 3 months of surgery. Such a design does not allow for residual microlesion effects in the postoperative period or the observed increase in stimulation efficacy over 3 months of continuous stimulation in open-label trials.

Our study shows a clear reduction in the headache frequency and severity of CCH attacks with

VTA-DBS, with greater benefit on frequency. However, using one aspect alone—headache severity or headache frequency—may not represent the real response of CCH attacks to an intervention. Therefore, this study introduces the concept of HAL that may provide a more meaningful measure of symptom severity. VTA-DBS resulted in significant improvement in the HAL as early as 3 months postoperatively, which continued until the final follow-up point.

Figure 3 Improvement in quality of life, disability, and mood

**p* ≤ 0.05. *p* Values are Bonferroni-corrected; they represent individual tests at each time point relative to baseline (number of comparisons = 2 for tests at 6 and 12 months). Median percentage of improvement in quality of life (Short Form-36, EuroQoL), disability (Migraine Disability Assessment Score [MIDAS], Headache Impact Test-6 [HIT-6]), and mood (Hospital Anxiety and Depression Scale-anxiety [HAD-A], Hospital Anxiety and Depression Scale-depression [HAD-D]). BDI-II = Beck Depression Inventory II; SF36-MCS = Short Form-36 mental summary score; SF36-PCS = Short Form-36 physical summary score.

Nevertheless, the clinical meaningfulness of HAL as a primary endpoint needs validation by studies in larger cohorts.

The monthly triptan intake of the group as a whole dropped by 57% (497 doses per month). Using current UK costing estimates,³⁰ this can be calculated to be a saving of £8,291 a month for the 21 patients or around £395 a month per patient on triptans alone.

None of the QoL, disability, and mood outcome measures deteriorated following surgery and a number improved significantly from baseline (HIT-6, SF-36 PCS, and EuroQol). The largest improvement was seen in the SF-36 PCS at 6 months.

Improvement in QoL measures did not have the same magnitude as that observed with HAL. The relatively long duration of the disease (average 15 years) may have resulted in socioeconomic and psychosocial adjustments to chronic illness that are unlikely to improve immediately following improvement in the headache symptoms. Other factors to consider are other comorbidities in our cohort of patients.

The brain region used for DBS was first described as a surgical target by Sano et al.,³¹ who performed stereotactic lesions in 51 patients with pathologically aggressive behavior. Although this area has been widely described as the posterior hypothalamus, the anatomical accuracy of this label has been contested. The mammillothalamic tract represents the posterior border of the hypothalamus and the target area lies posterior to this within the ventral tegmentum of the midbrain.^{27,32} This brain region has also been used as a target in DBS for depression.³³

Our general practice is to perform DBS surgery under general anesthesia when the brain target can be well visualized with MRI to guide electrode insertion.^{24,25} However, we elected to perform surgery under local anesthesia for the first 11 patients. This allowed intraoperative testing with macrostimulation to study any possible intraoperative side effects of stimulation. With higher voltages, these included tachycardia, raised blood pressure, vertical diplopia, and a feeling of panic or impending doom. These effects were reproducible in all tested patients. Once the procedure was well-established locally, we performed the surgery under general anesthesia, relying on MRI-verified targeting.

Limitations apply to any open-label study. A placebo effect cannot be excluded; however, this is unlikely to be large with follow-up over 1 year. Moreover, there were a number of incidents where attacks recurred when stimulation was inadvertently switched off.

The 6 patients who had a short-lasting or no response to ONS therapy prior to receiving DBS had a much higher failure rate and no overall

improvement in HAL. Furthermore, those who did respond to DBS showed a very modest improvement in HAL when compared to that seen across the entire patient group. Moreover, 2 of the 5 patients with bilateral CCH were nonresponders. A failure to respond to ONS and the presence of bilateral symptoms may be predictors of poor outcome following DBS; however, these patient subgroups are too small to draw any firm conclusions.

Lack of response to VTA-DBS in some patients has been reported in previous series in spite of well-positioned DBS electrodes.³² Despite an increase in HAL in these patients (figure 2B), our cohort of patients experienced significant improvement as a group. Further work into structural and functional connectivity may reveal underlying differences between responders and nonresponders, improving patient selection and outcome of DBS in CH.

This study suggests that MRI-verified VTA-DBS may be a safe and effective treatment for drug-refractory CCH and could be considered for suitable patients who fail conventional treatment. We also noted positive effects of DBS for CCH on patient-reported QoL, disability, and mood.

AUTHOR CONTRIBUTIONS

H.A.: statistical analysis and interpretation of data, drafting of the manuscript, and manuscript revision. S.M., S.L.: recruitment of subjects and acquisition of data. J.H., M.J.: interpretation of data and manuscript revision. M.H., M.M., L.Z.: study concept, recruitment of subjects, interpretation of data, and manuscript revision. Both senior authors (L.Z. and M.M.) contributed equally to the paper.

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DISCLOSURE

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