CASE REPORT

Robotic-arm stereotactic radiosurgery as a definitive treatment for gelastic epilepsy associated with hypothalamic hamartoma

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SUMMARY

Gelastic seizures, characterised by paroxysms of pathological laughter, are most often associated with an underlying hypothalamic hamartoma. This report describes the definitive treatment using stereotactic-radiosurgery for a teenaged child whose gelastic epilepsy was found refractory to various antiepileptic drugs. Since surgery was not consented to, the child was referred to us for stereotactic radiosurgery (SRS), which was delivered with robotic-arm -SRS to a dose of 30 Gy in five fractions in five consecutive days. A decrease in the frequency of seizures was noticeable as early as within a week, and at 12 months after the procedure, there has been a total cessation of seizures.

BACKGROUND

Hypothalamic hamartoma associated gelastic epilepsy characterised by episodes of ictal-laughter warrant timely treatment as they are known to progress into more serious forms of partial and general seizure disorders. Left untreated, these often progress to encephalopathy, associated with cognitive and psychological implications.^{1 2}

The described patient had initially been offered surgery but not consented due to his desire to eliminate the 'risk of operative mortality'. The alternative approach to surgery, that is, stereotactic irradiation has been claimed to be equally effective, though the volume of clinical evidence remains low due to the rarity of this condition.^{3 4}

The patient was treated with robotic-arm mounted linear accelerator based stereotactic radiosurgery system (RA-SRS) on the basis of MRI-based target delineation.

In response, a very rapid decrease in the frequency of seizures was observed, as early as within a week after the procedure. This is a significant observation given that seizures have been recorded to decrease on an average of 6 months as per previously published reports.^{4 5} Furthermore, at 12 months postprocedure, there has been total cessation of his symptoms.

CASE PRESENTATION

This report discusses the case of a 17-year-old boy who had been diagnosed with gelastic epilepsy associated with an underlying hypothalamic hamartoma (figure 1) since the age of 4 years. He had received various antiepileptic drugs (AEDs) across the years, all of which were only partially effective

in maintaining freedom from gelastic seizures. His symptoms subsequently became totally refractory to AED. However, his symptoms were initially confined to 'laughing fits', after he attained the age of 12 years, he began experiencing occasional episodes of generalised seizures too.

He was of normal intelligence with an average performance at school, with no cognitive impairments. There were no histories of precocious puberty, eating disorders, behavioural disorders, trauma or metabolic disorders. However, given the ineffectiveness of AEDs in preventing seizures, he was offered definitive treatment, given the risk of progression to epileptic encephalopathy. Since the patient desired to undergo a non-surgical approach for treatment, he was offered SRS with either the *GammaKnife* (SRS using a cobalt-60-based system) or the *CyberKnife* (radiosurgery using a linear accelerator mounted upon a robotic arm).

Despite the fact that the *GammaKnife* system is backed by decades of user experience in treatment of various intracranial conditions, the *Cyberknife* was preferred for the main reason that it does not require a skull fixation frame. The same would be required for treatment with *GammaKnife*, requiring invasive placement of a stereotactic frame which via screwing into the skull bone.⁶

Figure 1 Hypothalamic hamartoma (blue arrow) as visualised on an axial MRI (T2) slice.

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TREATMENT

For treatment planning, the patient was initially imaged with both MRI and CT scans, and the tumour volume was delineated upon the fused CT–MRI images, using *MIMVista*. The target volume amounted to 48.3 cc and the dose prescribed was 30 Gy in five fractions in five consecutive days. The prescription was made to the 85% isodose-line, with the maximum point dose within the volume being 1.59 times, and the minimum point dose within the prescription volume being 0.88 times that of the prescribed dose. The doses to the critical organs at risk were well within the tolerable limits; for example, the maximum point dose to the brainstem was limited to 12.4 Gy (figure 2).

During imaging and treatment, the patient was immobilised with a thermoplastic cast (non-invasive) and the treatment was performed without sedation or anaesthesia of any sort. During treatment, the tracking method used was ‘6D-Skull’, a technique that utilises intratreatment X-ray images to match a patient’s skull bony-anatomy with that of the images used during planning purposes. Each fraction was completed in about 25 min (including time taken for setup and treatment).

OUTCOME AND FOLLOW-UP

The patient reported a decrease in seizure activity as early as in the first week after treatment. The patient was noted to have a complete cessation of seizures at the third month after treatment. Imaging carried out at 3 months after completion of

treatment revealed significant changes (figure 3). On T2-weighted MRI, significant radiation induced oedema in and around the hamartoma was observed, signifying increased permeability and membrane damage. A comparison of pre- and post-treatment MR spectroscopy (MRS) revealed a return to normalcy of the abnormally high myo-inositol peak, and of the abnormally low *N*-acetyl-aspartate peak. Also, the post-treatment MRS revealed an increase in the lipid and lactate peaks, signifying onset of cell damage.

Currently, at 12 months post-treatment, the patient remains totally free of seizures, and with no hormonal or neurological side effects, has returned to normal activities of daily living.

DISCUSSION

Gelastic seizures, also known as ‘laughing seizures’, are most commonly due to hypothalamic hamartomas. A fit of gelastic seizure typically involves an episode of laughter, grinning or giggling. Some patients may also manifest crying (dyscrastic seizures). However, normal laughter often holds an emotional basis, the laughter seen in gelastic seizures are described as ‘mirthless laughter’, owing to the fact that patients do not experience ‘happiness’ that accompanies laughter. While some patients remain conscious during episodes of gelastic seizures, a majority of the patients are non-aware during an episode.^{7 8}

Given the rarity of this clinical condition, much remains to be answered regarding the pathogenesis and the origin of ictal

Figure 2 Visualisation of the stereotactic radiosurgery procedure, where each spike depicts an entering beamlet (A). Axial (B), sagittal (C) and coronal (D) slices demonstrating the target volume (pink outline), and its proximity to critical structures such as the brainstem. The green outline depicts the volume receiving 30 Gy. The yellow and the blue outlines depict the volumes receiving 27 Gy and 10.13 Gy respectively. Note that much of the brainstem is well outside the 10.13 Gy isodose line.

Figure 3 A comparison of pretreatment (A) and 12 weeks post-treatment (B) T2-weighted MRI showing significant postirradiation changes in and around the hypothalamic hamartoma (compare the orange and the blue arrows), signifying post-treatment oedema and increased fluidity. The pre-treatment and post-treatment MR-spectroscopy can be compared using (C) and (D). In the pretreatment analysis (C), an abnormally high myo-inositol (ml) peak and a depressed *N*-acetylaspartate (NAA) peak can be observed. In the post-treatment analysis (D), note the increased lactate and lipid spikes, signifying onset of radiation induced necrosis. Also can be seen are the reduction in the ml spike as well as an increase towards normalcy of the NAA spike.

laughter among patients with hypothalamic hamartomas. It was observed as recently as in 1995 that hypothalamic hamartomas *themselves* are the origin of ictal seizures.⁹

Hypothalamic hamartomas are congenital lesions comprising non-neoplastic aggregations of small and large neuron cells. It has recently been reported that the 'small neurons' in the hypothalamic hamartomas comprise approximately 90% of the neurons in a hypothalamic hamartoma.¹⁰ While the 'small neurons' have been demonstrated to possess intrinsic pacemaker firing activity, the large neurons are currently postulated to behave as excitatory projection neurons, and are thus assumed to facilitate functional outflow of seizures to the brain.^{10–12}

In a review of 100 patients with gelastic seizures,¹³ it was seen that all lesions were located in the posterior hypothalamus at the level of the mammillary bodies (figure 4). Patients who

had 'gelastic plus' seizures often had a significantly longer duration since onset than with patients who had gelastic seizures alone. It was observed that the volume of the mass had no correlation between gelastic alone against gelastic plus seizures.^{13–15}

Though a majority of the cases with gelastic epilepsy are known to have an underlying hypothalamic hamartoma, rare reports have also documented similar ictal laughter to be associated with other areas of the brain.¹⁷

Even though much remains to be explained with regards to pathogenesis and neuro-anatomical basis, it is very well understood at this time that gelastic epilepsy associated with hypothalamic hamartomas eventually become refractory to AED, and that episodes of ictal laughter are likely to progress to more generalised forms of seizures. Thus, it is clinically important to eliminate the focus of the ictal episodes at the earliest, to

Figure 4 MRI-based rendition depicting the relative location of the hypothalamic hamartoma (green mass) with respect to the mammillary bodies (brown masses).

prevent progression to generalised seizures and to avoid the risk of epileptic encephalopathy.¹⁶

Neurosurgical treatment by resection of the hypothalamic hamartoma was first documented in 1969.¹⁷ However, neurosurgeons remained unconvinced about the epileptogenicity of the hypothalamic hamartoma and thus continued temporal and frontal lobectomies based upon EEG recordings. After three unfortunate decades, only the work of Munari *et al* (in 1995)⁹ who utilised electrodes placed stereotactically into the hypothalamic hamartoma was able to convince the neurosurgical community of the epileptogenic potential of hypothalamic hamartoma. Surgical interventions largely attempt to attain either complete resections or disconnections.

Although various routes of surgical access have been utilised, given the location of the lesion (figures 4 and 5), the use of neurosurgery is associated with risks of morbidity which could be due to thalamocortical infarcts leading to serious morbidities such as hemiparesis, oculomotor disturbances, visual field

Figure 5 MRI reconstruction demonstrating the spatial location of the hypothalamic hamartoma.

deficits, memory loss, feeding disorders, diabetes insipidus and hypothyroidism. Furthermore, despite surgery, some patients do not attain total freedom from seizures and may require additional treatment with stereotactic irradiation. Recently, attempts to use brachytherapy and radiofrequency ablation to attain lesion destruction have been reported. However, being invasive procedures, they too hold similar risks associated with surgery.^{18 19}

SRS is increasingly being utilised since the past decade. The major attractions of stereotactic radiotherapy involve the avoidance of mortality and morbidity risks associated with invasive neurosurgery. The adjective stereotactic here implies the target localisation in relation to a fixed 3D reference system. Stereotactic localisation allows attainment of a high degree of accuracy and precision, enough to deliver a dose of radiation high enough to affect epileptogenesis while sparing critical normal structures at the same time. Stereotactic irradiation with the GammaKnife is performed with the use of a stereotactic frame of reference, which needs to be invasively fixed to the skull. For this reason, GammaKnife radiosurgery is almost always completed within a single large fraction. Frameless SRS is now possible with the integration of real-time image guidance technologies, as with the *Cyberknife*, *Novalis*, *Truebeam*, etc. The use of frameless SRS also allows fractionation of the procedure, meaning that the dose of radiation can be delivered over multiple installments, rather than a single large dose. This theoretically allows for better-sparing of critical normal structures.^{20 21}

The first treatment with radiosurgery was reported by Arita *et al* (in 1998),²² who utilised GammaKnife to deliver a single-fraction dose of 18 Gy. A dose-response relationship was later observed by Romanelli *et al*⁴ in a cohort of 10 patients treated with GammaKnife SRS, with all patients receiving lesion marginal dose >17 Gy achieving complete seizure freedom, and all patients receiving lesion margin dose <13 Gy requiring re-treatment.

Duration since onset has been reported to be another factor predictive of outcomes with SRS. Patients with short durations are likely to enjoy better responses, whereas patients with long histories are likely to receive modest benefits even with high doses.²³

The advent of frameless SRS has allowed the use of multiple fraction treatments, which allows the delivery of equivalent or higher doses of radiation to the target, while reducing the chances of normal tissue complications. However, the main attraction of frameless SRS is the total non-invasiveness of the procedure, since it eliminates the need for a stereotactic skull frame that needs to be invasively attached to the skull with GammaKnife SRS.

Jean Regis *et al* prospectively analysed 60 patients between 1999 and 2005, treated with GammaKnife.²⁴ All patients had benefit, with 37% patients being completely seizure free at a follow-up for more than 3 years. No instance of permanent neurotoxicity was observed. However, three patients experienced poikilothermia which was transient.²⁴

The main disadvantage of SRS in comparison to surgery is that the response after SRS has a latent period, with maximal effect usually experienced after a lag period of about 6 months post-treatment. However, our case is unique in that the response has been almost immediate. Surgery may be preferred over radiosurgery among patients with very large lesions that could be causing symptoms due to mass effect, since surgery can accomplish immediate decompression.²⁵

Given the rare nature of the lesion it is unlikely that large randomised trials to compare surgery against stereotactic irradiation will ever be feasible. Given that the demonstration of

epileptogenicity of hypothalamic hamartoma in the causation of gelastic seizures was made as recently as in 1995, the feasibility of a retrospective comparison of surgery against SRS is seemingly difficult. Also, no trials have been performed to compare single fraction against multiple fraction treatments.

Learning points

- ▶ Hypothalamic hamartomas are non-neoplastic lesions that are known to be epileptogenic for gelastic seizures.
- ▶ Gelastic seizures are known to become refractory to antiepileptic drugs, and over time are known to progress to more complex seizure syndromes including generalised seizures and epileptic encephalopathy.
- ▶ The treatment of hypothalamic hamartomas with radiosurgery is known to be as effective as neurosurgery, while also being safer.
- ▶ The advent of image-guidance and robotic-arm radiosurgery allows non-invasive treatment without the requirement of invasive fixation of stereotactic frames which were needed with the older GammaKnife radiosurgery systems.
- ▶ The advent of frameless linear-accelerator-based radiosurgery has also allowed the use of multifraction approach instead of the single fraction treatment which was practiced with older GammaKnife radiosurgery systems. This allows for better sparing of critical normal organs from high effective doses.

Contributors SPS identified the case as worthy of reporting. SR wrote the initial version of the manuscript. GJM provided the images and performed a literature review. AB finalised the article.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Ironside R. Disorders of laughter due to brain lesions. *Brain* 1956;79:589–609.
- 2 Berkovic SF, Andermann F, Melanson D, *et al.* Hypothalamic hamartomas and ictal laughter: evolution of a characteristic epileptic syndrome and diagnostic value of magnetic resonance imaging. *Ann Neurol* 1988;23:429–39.
- 3 Unger F, Schrötnner O, Feichtinger M, *et al.* Stereotactic radiosurgery for hypothalamic hamartomas. *Acta Neurochir Suppl* 2002;84:57–63.
- 4 Romanelli P, Muacevic A, Striano S. Radiosurgery for hypothalamic hamartomas. *Neurosurg Focus* 2008;24:E9.
- 5 Kida Y, Yoshimoto M, Hasegawa T. Radiosurgery of hypothalamic hamartomas. *No Shinkei Geka* 2008;36:225–32.
- 6 Unger F, Schrötnner O, Haselsberger K, *et al.* Gamma knife radiosurgery for hypothalamic hamartomas in patients with medically intractable epilepsy and precocious puberty. Report of two cases. *J Neurosurg* 2000;92:726–31.
- 7 Arroyo S, Lesser RP, Gordon B, *et al.* Mirth, laughter and gelastic seizures. *Brain* 1993;116:757–80.
- 8 Shin HY, Hong SB, Joo EY, *et al.* Gelastic seizures involving the right parietal lobe. *Epileptic Disord* 2006;8:209–12.
- 9 Munari C, Kahane P, Francione S, *et al.* Role of the hypothalamic hamartoma in the genesis of gelastic fits (a video-stereo-EEG study). *Electroencephalogr Clin Neurophysiol* 1995;95:154–60.
- 10 Wu J, DeChon J, Xue F, *et al.* GABA(A) receptor-mediated excitation in dissociated neurons from human hypothalamic hamartomas. *Exp Neurol* 2008;213:397–404.
- 11 Wu J, Xu L, Kim DY, *et al.* Electrophysiological properties of human hypothalamic hamartomas. *Ann Neurol* 2005;58:371–82.
- 12 Kim do Y, Fenoglio KA, Simeone TA, *et al.* GABAA receptor-mediated activation of L-type calcium channels induces neuronal excitation in surgically resected human hypothalamic hamartomas. *Epilepsia* 2008;49:861–71.
- 13 Parvizi J, Le S, Foster BL, *et al.* Gelastic epilepsy and hypothalamic hamartomas: neuroanatomical analysis of brain lesions in 100 patients. *Brain* 2011;134:2960–8.
- 14 Oehl B, Brandt A, Fauser S, *et al.* Semiologic aspects of epileptic seizures in 31 patients with hypothalamic hamartoma. *Epilepsia* 2010;51:2116–23.
- 15 Abou-Khalil BV. Hypothalamic hamartomas—what determines seizure types and other clinical manifestations? *Epilepsy Curr* 2012;12:59–60.
- 16 Striano S, Striano P, Sarappa C, *et al.* The clinical spectrum and natural history of gelastic epilepsy-hypothalamic hamartoma syndrome. *Seizure* 2005;14:232–9.
- 17 Paillas JE, Roger J, Toga M, *et al.* Hamartoma of the hypothalamus. Clinical, radiological and histological study. Results of excision. *Rev Neurol (Paris)* 1969;120:177–94.
- 18 Parrent AG. Stereotactic radiofrequency ablation for the treatment of gelastic seizures associated with hypothalamic hamartoma. Case report. *J Neurosurg* 1999;91:881–4.
- 19 Schulze-Bonhage A, Ostertag C. Treatment options for gelastic epilepsy due to hypothalamic hamartoma: interstitial radiosurgery. *Semin Pediatr Neurol* 2007;14:80–7.
- 20 Collen C, Ampe B, Gevaert T, *et al.* Single fraction versus fractionated linac-based stereotactic radiotherapy for vestibular schwannoma: a single-institution experience. *Int J Radiat Oncol Biol Phys* 2011;81:e503–9.
- 21 Debus J, Pirzkall A, Schlegel W, *et al.* Stereotactic one-time irradiation (radiosurgery). The methods, indications and results. *Strahlenther Onkol* 1999;175:47–56.
- 22 Arita K, Kurisu K, Iida K, *et al.* Subsidence of seizure induced by stereotactic radiation in a patient with hypothalamic hamartoma. Case report. *J Neurosurg* 1998;89:645–8.
- 23 Mathieu D, Kondziolka D, Niranjan A, *et al.* Gamma knife radiosurgery for refractory epilepsy caused by hypothalamic hamartomas. *Stereotact Funct Neurosurg* 2006;84:82–7.
- 24 Régis J, Scavarda D, Tamura M, *et al.* Epilepsy related to hypothalamic hamartomas: surgical management with special reference to gamma knife surgery. *Childs Nerv Syst* 2006;22:881–95.
- 25 Palmini A, Chandler C, Andermann F, *et al.* Resection of the lesion in patients with hypothalamic hamartomas and catastrophic epilepsy. *Neurology* 2002;58:1338–47.

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