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Gelastic epilepsy and hypothalamic hamartomas: neuroanatomical analysis of brain lesions in 100 patients

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Hypothalamic hamartomas present with isolated fits of ictal laughter (gelastic epilepsy) or a combination of gelastic and other types of seizures. Many of these patients also suffer from cognitive decline, neuropsychiatric comorbidities and precocious puberty. Although there is a large body of anecdotal evidence about hypothalamic hamartomas and gelastic seizures, many questions still remain to be answered. For instance, which specific hypothalamic regions are most affected by the location of hamartomas causing laughing versus other types of seizures? Does the neuroanatomical localization of the lesions differ in cases with only gelastic seizures or a combination of gelastic and other types of seizures? Does the location of the lesions correlate with the presence of precocious puberty, and does the type of lesion influence the severity or the type of seizures? In a retrospective review of clinical and structural neuroimaging data from 100 cases of gelastic epilepsy and hypothalamic hamartoma, we aimed to address these questions by analysing the clinical presentation and the neuroanatomical features of the hypothalamic lesions in these patients. Our findings suggest that in all 100 cases, lesions were centred at the level of the mammillary bodies in the posterior hypothalamus. Compared with the patients with pure gelastic seizures ($n = 32$), those with gelastic and other types of seizures ($n = 68$) had significantly longer duration of epilepsy ($P < 0.001$), whereas age of seizure onset, the volume of lesions and the proximity to the mammillary bodies were not different between the two groups. In contrast, patients with cognitive or developmental impairment and those with precocious puberty had significantly larger lesions involving the anterior and posterior hypothalamus.

Keywords: laughter; epilepsy; brain and behaviour; subcortical seizures; hypothalamus
Abbreviations: DQ = developmental quotient

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Introduction

Investigations into the role of the hypothalamus in emotional expression date back to the early 20th century when it was discovered that the stimulation of this subcortical structure elicited a response in the sympathetic nervous system (Karplus and Kreidl, 1909). Building upon this knowledge, Cannon and Reymert (1928) discovered that the stimulation of the hypothalamus in decerebrate cats would show an uncontrollable rage in response to minor sensory stimuli, a condition that he coined 'sham rage' since it was not directed towards the triggering stimulus. Cannon's student, Philip Bard (1928) then showed that this sham rage depended upon the integrity of the hypothalamus.

Another link between the hypothalamus and emotional expression stems from observations in patients with laughing or gelastic epilepsy. These patients exhibit stereotypical behaviour of mirthless laughter during their ictal events. Although seizures originating from various brain sites (such as the temporal, frontal or parietal lobes) may cause laughter (Ironside, 1956; Mutani *et al*., 1979; Arroyo *et al*., 1993; Satow *et al*., 2003; Shin *et al*., 2006), gelastic epilepsy is most classically related to hypothalamic hamartomas. The majority of patients with hypothalamic hamartomas develop epilepsy that evolves into multiple seizure types including focal or generalized seizures and concomitant cognitive decline and neuropsychiatric comorbidities (Berkovic *et al*., 1988; Kerrigan *et al*., 2005). Patients with hypothalamic hamartomas often become refractory to medications and require surgical treatment with resection, gamma knife or interstitial radiosurgery (Regis *et al*., 2000; Schulze-Bonhage and Ostertag, 2007).

Utilizing intracranial electrodes for seizure monitoring, Munari and colleagues (1995) made a seminal observation that hypothalamic hamartomas are the origin of ictal discharges for gelastic seizures. Subsequent studies have verified the intrinsic epileptogenicity of the hamartomas and suggested that electrical stimulation of the hypothalamic hamartomas reproduce typical gelastic events while the resection or stereotactic radiofrequency lesioning of the hamartomas result in seizure remission (Cascino *et al*., 1993; Kuzniecky *et al*., 1997; Fukuda *et al*., 1999; Vera *et al*., 1999; DiFazio and Davis, 2000; Kahane *et al*., 2003; Homma *et al*., 2007; Kameyama *et al*., 2009, 2010).

The hypothalamic hamartoma lesions are focal congenital tumours composed of cytologically normal, small and large neurons, which are organized in poorly demarcated clusters of variable size and density (Coons *et al*., 2007). In a study of surgically resected tissue by Wu and colleagues (2005), it was shown that small hypothalamic hamartoma neurons (which make up ~90% of the hypothalamic hamartoma neuron population) are predominantly GABAergic and exhibit an interneuron-like phenotype, while also demonstrating intrinsic pacemaker firing activity (Wu *et al*., 2005). Conversely, large hypothalamic hamartoma neurons are much less abundant, and possess the functionally immature property of depolarizing and firing in response to GABA ligands, most likely resulting from reversal of the transmembrane chloride gradient (Kim *et al*., 2008, 2009; Wu *et al*., 2008). The large hypothalamic hamartoma neurons are likely excitatory projection neurons, and therefore may mediate functional outflow of seizure activity from the hypothalamic hamartomas to the brain, resulting in clinical symptoms. However, the exact nature of this connection remains unknown.

These findings beg the question of why hamartomas cause seizures with the specific ictal behaviour of laughter? What are the exact functional pathways that connect the hypothalamic hamartomas to the adjacent normal hypothalamic, or perhaps remote non-hypothalamic structures? While the question of epileptogenesis is outside the scope of our study, we aim to address the second question by analysing the neuroanatomy of hypothalamic lesions in more detail. The rationale for this anatomical analysis is 2-fold: (i) the stereotypy of ictal behaviour is due to the propagation of ictal discharges along precise neuroanatomical pathways involving a specific neuroanatomical network and (ii) each part of the hypothalamus contains distinct nuclei that have well-described unique anatomical connections (Saper, 2003). Thus knowing the specific anatomical location of the usually well-defined single lesions in patients with hypothalamic hamartomas and gelastic epilepsy will help us generate hypotheses about the possible involvement of specific hypothalamic nuclei and neuroanatomical routes of seizure propagation in these cases. Motivated by this, the current study aimed to address the following questions: do hypothalamic hamartomas localize to a particular region of the hypothalamus and the vicinity of any specific hypothalamic nuclei? Does the location or the volumetric dimensions of the lesions in gelastic epilepsy differ in cases with or without other types of seizures, with or without precocious puberty and with or without cognitive impairment?

Materials and methods

One hundred cases were included from Barrow Neurologic Institute Hypothalamic Hamartoma Centre. These cases were included from a larger pool of patients with hypothalamic hamartomas. We excluded cases with (i) genetic syndromes, such as Pallister–Hall syndrome; (ii) any prior history of surgical intervention; (iii) any prior history for gamma knife radiosurgery; and (iv) any other brain abnormality on the imaging study besides the hypothalamic hamartomas. It is important to note that our cohort included patients with hypothalamic hamartomas who had been referred to our Institute for the treatment of seizures and thus did not include any cases of hypothalamic hamartomas without seizures. Patients with clinically symptomatic hypothalamic hamartomas (but without seizures) are often referred to endocrinology services for the evaluation of precocious puberty and are seldom evaluated in neurology or epilepsy clinics.

Most patients had video-EEG monitoring at the referring centres. Data from seizure monitoring and clinical interviews were used to determine seizure type(s) and frequency. All patients had been thoroughly evaluated for their IQ or developmental quotient (DQ), as described previously (Prigatano *et al*., 2008). All patients were evaluated by an endocrinologist as part of their pre-surgical workup. In patients who were referred after the age of 12 years, we used clinical history rather than formal endocrinological evaluations to determine if they had suffered from precocious puberty.

We systematically examined the structural preoperative MRIs to identify the hypothalamic harmartomas in all patients using coronal T_1-weighted, T_2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. The images were collected from brain MRIs that were already identified to have a hypothalamic hamartoma by a neuroradiologist with the typical appearance of T_1-hypointensity and T_2-hyperintensity. Two neurologists examined all magnetic resonance images of the lesions and systematically entered the data into a spreadsheet. Information obtained for each patient included slice thickness in the coronal series and the morphology using the criteria defined by Delalande Grades I–IV hypothalamic hamartoma classification (Delalande and Fohlen, 2003). The hamartomas were categorized by their location within the hypothalamus as right, left or bilateral and also by the asymmetry of attachment or location. On coronal images, the extent of the anterior to posterior dimensions of the hypothalamic hamartomas was determined in relation to the location of the mammillary bodies, which was marked as the reference slice '0'. The rationale for using mammillary bodies as the point of reference is the ease with which these nuclei can be identified. One slice anterior to the mammillary bodies was marked '+1', and one slice posterior to the mammillary bodies was marked '−1'. In each case, the number of slices was multiplied by the slice thickness and added to the total interslice distance to estimate the dimensions from the mammillary bodies level. The distance between the most lateral and medial margins of the hypothalamic hamartomas were measured to the nearest millimetre in order to determine the lateral extent of the lesion, whereas the distance from the most dorsal point of the lesion to its most ventral point was measured to determine the ventrodorsal or vertical extent of the lesion. The distance from the most lateral edge of the lesion to the mid-ventricular vertical line was used to determine the lateral extent of the lesion, whereas the distance from the most dorsal edge of the lesion to the floor of the ventricle was used to determine the ventrodorsal extent of the lesion.

The volume of the lesion was estimated by using the equation [Lesion volume (cm^3) = (π.W*H*L)/6] where 'W' was the width or the largest horizontal diameter (measured on coronal view), 'H' was the largest measured vertical distance (measured on coronal view) and 'L' was the largest anterior to posterior length of the hypothalamic hamartoma (measured on sagittal view). In our statistical analysis, we applied Fisher's exact test for categorical data and t-test and ANOVA for continuous data using the significance level of $P < 0.05$.

Results

Clinical findings

Among the 100 identified cases, 41 patients were female and 59 were male (Table 1). These two groups did not differ significantly from each other in the methods of imaging acquisition [i.e. thickness of magnetic resonance slices ($P = 0.09$) or the interslice distance ($P = 0.07$)], the anatomical location of the hypothalamic hamartoma lesion [i.e. distance anterior ($P = 0.89$) or posterior ($P = 0.35$) to the level of mammillary bodies], the size of the lesion [i.e. the diameter of the hypothalamic hamartoma lesion in vertical ($P = 0.42$) or horizontal planes ($P = 0.44$), the 3D volume of hypothalamic hamartoma ($P = 0.37$) or the area of hypothalamic hamartoma base attachment ($P = 0.51$)]. However, we found a clear difference in the length of time from the diagnosis to surgery between females and males even though the age of onset of seizures was not significantly different between the two groups. Overall, the female patients had ~60 months' longer wait ($P < 0.02$, independent samples t-test) from the time of diagnosis to surgery compared with their male counterparts despite the fact that they had a similar age of onset of seizures: 8.95 ± 14.8 months (mean ± standard deviation) in females versus 11.6 ± 20.17 months in males ($P = 0.45$, independent samples t-test). Given these findings, we decided to carry out the rest of the analyses by merging the two gender groups together.

Overall, the age of seizure onset in patients with hypothalamic hamartomas was 10.52 ± 18.12 months. In general, there was a mean delay of 133.2 ± 126.7 months between the reported onset of seizures and the date of preoperative brain MRI scan.

Although all cases had gelastic seizures or a prior history of gelastic seizures, there were 68 patients, designated as 'gelastic

Table 1 Study Cohort

Clinical feature	Gelastic only	Multiple seizure types	Significance, *P*-value
Number of patients	32	68	
Age at time of imaging	68.2 months	179.0 months	<0.0001*
Gender (% Female)	41	41	
Treatment-resistant epilepsy (%)	100	100	
Age at seizure onset	8.5 months	12.2 months	0.33*
Duration of epilepsy	61.3 months	167.1 months	<0.0001*
Daily seizures (%)	91	88	
Anti-epileptic drugs at time of imaging	1.4	2.0	0.001*
Developmental delay/cognitive impairment (%)	28	50	0.052**
History of central precocious puberty (%)	25	21	0.62**

*Student's t-test.
**Fisher's exact test two tailed.

epilepsy-plus', who had both gelastic and other seizure types including partial and generalized seizures. In the cohort, 43% of the patients had cognitive or developmental impairment defined by IQ or DQ <70. However, central precocious puberty was concurrently present in only 21% of the patients. As noted, we did not include patients with the genetic syndrome of Pallister–Hall in our cohort.

Patients with gelastic epilepsy-plus suffered from multiple types of epilepsy. These were gelastic (at time of evaluation or at some time during their clinical course, $n = 100$), complex partial seizures ($n = 49$), generalized tonic–clonic seizures ($n = 26$), simple partial (not gelastic, $n = 2$), atonic ($n = 2$), tonic ($n = 5$) and infantile spasms ($n = 4$). Comparative analysis of the available clinical data from patients with gelastic epilepsy only and those with multiple types of seizures (i.e. the gelastic epilepsy-plus group) revealed statistically significant differences in age and duration of epilepsy (Table 1).

Patients' seizure frequency had a heterogeneous profile. While the majority of patients ($n = 90$) had daily seizures (range 1 to >100 per day), only a minority of patients had less severe epilepsies (nine had at least one seizure per week, but not daily, and one had at least one seizure per month, but not every week).

All patients in our cohort were refractory to medical management defined as frequent breakthrough seizures despite trials of three anti-epileptic drugs in therapeutic doses and full compliance.

Magnetic resonance imaging findings

The lesions were categorized by the Delalande classifications I–IV (Fig. 1). Overall, the most common Delalande type in the cohort was Type II (54%) with a vertical plane of attachment within the third ventricle. Type III was next most common type at 32% with a plane of attachment on both sides of the floor of the third ventricle with a vertical plane of attachment within the ventricle, and horizontal plane of attachment to the underside of the hypothalamus.

The hypothalamic hamartoma lesions showed a wide distribution in their lateralization with attachment to the right side of the hypothalamus in 28%, left-sided attachment in 32% and bilateral attachment in 40%.

The anatomical dimensions of the hypothalamic hamartomas were also measured in three planes: vertical, horizontal and anterior–posterior. The vertical extent of the hypothalamic hamartomas ranged from 0.49 to 3.63 cm (mean ± SD, 1.4 ± 0.66). The largest horizontal diameter in the coronal plane ranged from 0.41 to 3.74 cm (mean ± SD, 1.17 ± 0.62). The horizontal diameter of the hypothalamic hamartoma was also measured laterally from the centre of the third ventricle and extended on average 0.54 ± 0.32 cm to the left and 0.52 ± 0.29 cm to the right. In addition, the anterior to posterior distance ranged from 0.3 to 2.75 cm (mean ± SD, 1.26 ± 0.57). The mean lesion volume was measured as 1.49 ± 2.28 cm^3. Likewise, the base surface area (i.e. the area of lesion attachment to the hypothalamus) was 0.80 ± 0.58 cm^2 and the base area/volume ratio was 1.2 ± 0.92 cm^{-1}.

In order to analyse if the difference in the type of seizures could be explained by any of the variables, we examined the effect of each variable between the two groups of patients on the basis of seizure types. In our cohort, 32 patients had gelastic epilepsy-only seizures and 68 patients had gelastic epilepsy-plus, i.e. they reported multiple seizure types including gelastic and non-gelastic types. We found no significant difference between the gelastic epilepsy and gelastic epilepsy-plus groups in age of onset ($P = 0.16$), vertical ($P = 0.56$) or horizontal ($P = 0.83$) or anterior–posterior extent of the lesion ($P = 0.50$), volume ($P = 0.34$), surface area of hypothalamic hamartoma attachment ($P = 0.96$), relative ratio of hypothalamic hamartoma base area to its volume ($P = 0.63$) or location of the lesion in relation to the mammillary bodies ($P = 0.72$). Likewise, methodological parameters such as the thickness ($P = 0.99$) or the interslice distance ($P = 0.81$) between magnetic resonance slices were the same in both groups. The only parameter that was different between the two groups was the duration of epilepsy i.e. from the time of first seizure activity to the time of surgery ($P < 0.001$), which was a mean duration of 61.3 ± 48.6 months for the gelastic epilepsy group compared with 167.1 ± 137.9 months for the gelastic epilepsy-plus group.

We also compared the same variables between the groups of patients with IQ or DQ < 70 ($n = 43$) and those with IQ or DQ ⩾70 ($n = 57$). Patients with IQ/DQ < 70 had significantly larger volume ($P < 0.041$), surface area of base of attachment ($P < 0.03$), vertical ($P < 0.008$), horizontal ($P < 0.042$) and anterior–posterior distances ($P < 0.04$) of hypothalamic hamartomas lesions.

Comparing the groups with ($n = 21$) and without precocious puberty ($n = 79$) yielded similar results i.e. the group with precocious puberty had significantly larger volumes ($P < 0.001$), bases of attachment ($P < 0.005$), base/volume ratios ($P < 0.0001$), vertical ($P < 0.001$), horizontal ($P < 0.001$) and anterior–posterior diameters ($P < 0.001$) of the hypothalamic hamartomas. The lesions were also significantly larger in the posterior dimensions extending posterior to the mammillary bodies (4.48 ± 2.84 mm in

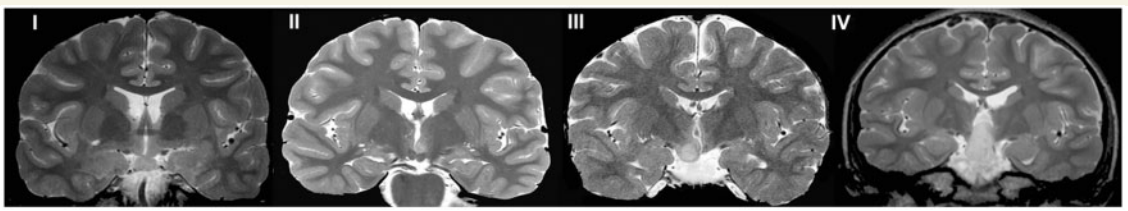

Figure 1 Delalande types. Type I has a horizontal orientation and may be lateralized on one side; Type II has a vertical orientation and an intraventricular location; Type III is a combination of types I and II; Type IV is a giant hamartoma.

the group with and 2.87 ± 1.52 mm in the group without precocious puberty, $P < 0.002$).

We tested a possible relationship between the Delalande type and the volume as well as duration of the disease, and found that the volume of the lesion was significantly different among various Delalande types of hypothalamic hamartomas [df 3, 96; F (45,15); $P < 0.001$], whereas the duration of the disease had no effect on the type of lesion [df 3, 96; F (1, 41); $P = 0.25$].

Regardless of the type of seizures (gelastic epilepsy-only or gelastic epilepsy-plus), or the presence of precocious puberty or cognitive impairment, we found no correlation between the duration of disease and the volume of hypothalamic hamartoma lesions ($P = 0.87$).

Taking into account slice thickness and interslice distance in each case, we visualized the distribution of the lesion locations using the mammillary level as the point of reference. As seen in Fig. 2, this analysis revealed that in all 100 cases (100%), the hypothalamic hamartoma lesions crossed the level of the mammillary bodies.

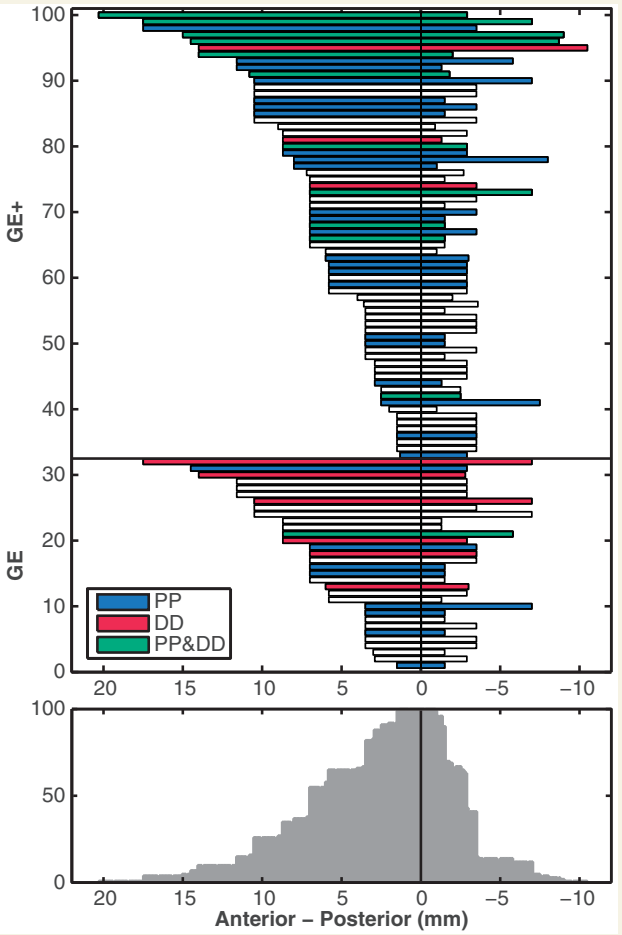

Figure 2 Anterior–posterior extent of lesions. Using the mammillary bodies as the point of reference (Point 0 on the *x*-axis), we measured the distance to the posterior (negative) and anterior (positive) edge of the lesions in patients with gelastic epilepsy-only ($n = 32$) and gelastic epilepsy-plus (GE^+; $n = 68$) with precocious puberty (PP), developmental delay (DD; defined as IQ or DQ <70). In 100% of the cases (*y*-axis), hypothalamic hamartomas were located at the level of the mammillary bodies. The skew of the lower plot may be related to the larger size of the hypothalamic space anterior to the mammillary bodies. Seizure groups in the top plot on the *y*-axis: pure gelastic epilepsy, and gelastic epilepsy-plus. Colours: blue = patients with precocious puberty; red = patients with developmental delay; green = patients with precocious puberty and developmental delay.

Discussion

Significant findings

Our analysis yielded some positive and pertinent negative findings: (i) in all patients, the hypothalamic hamartoma lesions involved the hypothalamus at the level of the mammillary bodies; (ii) longer duration of epilepsy (rather than the location or size of lesions) determines the development of other seizure types; (iii) patients with cognitive impairment and patients with precocious puberty had significantly larger lesions that extended significantly further in all planes, and (iv) there was no correlation between lesion volume and duration of epilepsy.

Hypothalamic lesions and cognitive impairment or precocious puberty

Our findings are in line with previous case reports and studies conducted in a smaller case series. For instance, in a study of MRIs obtained from patients with hypothalamic hamartomas, Debeneix and colleagues (2001) compared the anatomical features of the lesions in patients with isolated precocious puberty (nine patients), to patients with a combination of precocious puberty and seizures (five patients), or with isolated seizures (four subjects). They found that patients with isolated endocrine issues had pedunculated lesions suspended from the floor of the third ventricle whereas all patients with neurological symptoms had sessile lesions located in the interpeduncular cistern with extension to the hypothalamus. Other studies in a few patients have also reported smaller isolated lesions confined to the anterior hypothalamus that are associated with precocious puberty without seizures (Barral *et al*., 1988; Boyko *et al*., 1991; Mahachoklertwattana *et al*., 1993; Inoue *et al*., 1995). In other studies, the hypothalamic hamartoma lesions with pituitary stalk contact were shown to be associated with central precocious puberty (Freeman *et al*., 2004; Prigatano *et al*., 2008; Chan, 2010). Furthermore, previous studies have analysed the gross anatomical locations of hypothalamic hamartomas and have made the observation that parahypothalamic lesions were predominantly associated with precocious puberty whereas intrahypothalamic lesions were mainly associated with gelastic epilepsy and cognitive, behavioural and psychiatric disease (Arita *et al*., 1999). Often the parahypothalamic lesions were larger, had contact with the pituitary stalk and were more commonly associated with precocious puberty without other neurological manifestations (Arita *et al*., 1999; Kerrigan *et al*., 2005; Harvey and Freeman, 2007). In contrast, the intrahypothalamic hamartomas were sessile and had either partial or complete broad-based attachment to the

surrounding tissue, which correlated more with epilepsy and cognitive impairment (Polkey, 2003; Maixner, 2006; Coons *et al*., 2007).

Since our cohort did not include patients with precocious puberty without seizures, or cognitive impairment without seizures, and because the issues of precocious puberty and cognitive impairment were not the main focus of our study, we did not perform systematic comparison of the structural abnormalities in patients with and without precocious puberty or cognitive impairment. However, our overall findings are compatible with prior studies and suggest that the larger size of hypothalamic hamartoma lesions distinguish patients with cognitive impairment and precocious puberty from those without. Based on this finding, we hypothesize that the larger bulk of disorganized tissue (or the more structural distortion of the hypothalamus by larger lesions) could be involved in the pathogenesis of cognitive and endocrine comorbidities. Although the same volume effect was seen in both sets of patients, we are mindful that this similarity does not necessarily imply a biological linkage between the two comorbidities, but simply indicates that both are a function of the size of the tumour. Parallel to previous observations that anterior contact with pituitary stalk may contribute to the development of precocious puberty, in our cohort, all cases with precocious puberty had lesions that were significantly larger in the anterior extent of the lesions.

Pure gelastic epilepsy versus multiple seizure types

Previous reports in the medical literature have drawn an association between larger hamartomas and increased seizure severity (Freeman *et al*., 2004; Kerrigan *et al*., 2005; Harvey and Freeman, 2007). However, our study suggests that size and volume parameters were not correlated with the type of seizures. As noted, the size of the hypothalamic hamartoma lesions was the same in patients with pure gelastic epilepsy compared with patients with gelastic epilepsy and other types of seizures. However, in patients with gelastic epilepsy-plus, we found a significantly older age and longer duration of disease (measured in our cohort as the time lag between the onset of seizures and the time of preoperative neuroimaging). This finding likely reflects the natural history of the disease consistent with the hypothesis that age, rather than the size of the lesion, is the major risk factor for worsening of seizures (Berkovic *et al*., 1988). This finding is also consistent with the available evidence from recent semiological studies in patients with gelastic epilepsy (Oehl *et al.,* 2010).

In our cohort, patients with older age and longer duration of the disease were referred for surgical evaluation with a significantly longer 'delay' from the time of diagnosis. This is likely due to the fact that surgical treatment of hypothalamic hamartomas has been available at specialized centres only over the past 10 years, and consequently treatment could be offered recently to relatively large numbers of previously untreated patients with hypothalamic hamartomas.

Of note, the mean duration of disease did not vary in a statistically significant way in terms of Delalande type or the volume of lesions, implying that the lesions remain relatively stable in size over time. In keeping with this, Oehl and colleagues (2010) made a similar observation that seizure semiology in patients with gelastic epilepsy is highly age dependent even though the size or location of hypothalamic hamartomas does not change with age. This suggests that the evolution of multiple seizure types may not be due to a larger size or mass effect of hypothalamic hamartoma lesions but may be related to altered networks or changes external to the hypothalamic hamartomas (e.g. in the rest of the brain) that may occur over time. This view is compatible with the notion of progressive worsening of seizures with time (Arita *et al*., 1999), and secondary epileptogenesis (Freeman *et al*., 2003), and the notion of gelastic epilepsy being associated with an underlying severe but potentially treatable encephalopathy (Striano *et al*., 2005, 2009). It has been suggested that gelastic epilepsy can be viewed as a spectrum of conditions with various degrees of severity ranging from previously normal children with gelastic epilepsy evolving towards a catastrophic symptomatic generalized epilepsy or partial epilepsy with cognitive impairment (Striano *et al*., 2009).

The posterior hypothalamus and laughing seizures

In line with the findings by Freeman and colleagues (2004), we found that 100% of the cases with gelastic epilepsy and hypothalamic hamartomas had involvement of the more posterior aspect of the hypothalamus at the level of the mammillary bodies (Fig. 3). We believe future studies of hypothalamic hamartomas may reveal the identity of nuclei that are at the core of seizure propagation from hypothalamic hamartomas to the other brain structures.

While the mammillary bodies themselves project heavily to the anterior nucleus of the thalamus [which in turn has access to greater limbic lobe of the brain and its target structures (Heimer and Van Hoesen, 2006)], there are other posterior hypothalamic nuclei (e.g. the ones with orexin and melanin concentrating hormone neurons) that project to mediodorsal nucleus of the thalamus and the adjacent intralaminar nuclei (Saper, 1996, 2003). In addition, lateral posterior hypothalamic nuclei in rodents have been found to be glutamatergic and project heavily to the basal forebrain and limbic system, particularly to the dentate gyrus and CA-2 of the hippocampus (Saper, 2003). There is also evidence that the nuclei in the posterior hypothalamus project directly to the brainstem (Bandler and Tork, 1987) and the cerebellum (Haines *et al*., 1990; Onat and Cavdar, 2003; Zhu *et al*., 2006), involvement of which has been implicated in the generation of pathological laughter (Parvizi *et al*., 2001, 2009). While some investigators have suggested that the anterior nuclei of the thalamus are critical for the propagation of seizure activity from the hypothalamus (Freeman *et al*., 2004), others have shown possible involvement of the mediodorsal nuclei of the thalamus (Kameyama *et al*., 2010) using single-photon emission computed tomography imaging. Although functional imaging studies are invaluable in determining the source of seizure activity (Mazziotta and Engel, 1984; Meyer, 2000; Ryvlin *et al*., 2003; Brandberg *et al*., 2004;

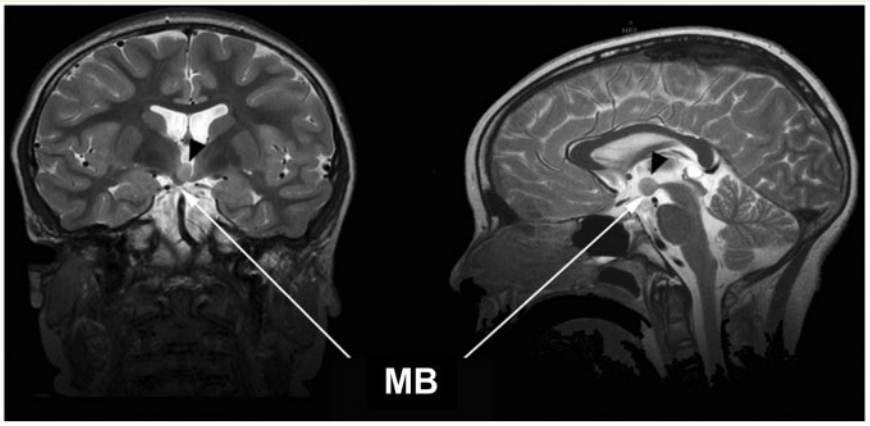

Figure 3 Proximity of lesions to the mammillary bodies. This figure illustrates how the hypothalamic hamartoma in this patient is adjacent to the mammillary body (MB). In our cohort, we found the same proximity in all 100 cases, although the shape of the hypothalamic hamartoma differs in each case depending on the type of lesion (Fig. 1). This patient is an 11.2-year-old male, with onset of gelastic seizures at 3 months of age. At the time of evaluation, he was having 6–8 seizures per day, with multiple seizure types, including gelastic, complex partial and generalized tonic–clonic seizures. He is developmentally normal and does not have a history of central precocious puberty.

Palmini *et al*., 2005; Salmenpera and Duncan, 2005; Shahar *et al*., 2008), one should be mindful of the reliance of these imaging methods on intersubject spatial normalization and group analysis (Van Essen and Dierker, 2007), which could significantly obscure their anatomical resolution. However, imaging methods with better spatial resolution such as functional MRI combined with anatomically more precise method of optogenetics (Lee *et al*., 2010) offer a novel and promising method by which the network circuitries of each hypothalamic region (relevant to gelastic epilepsy) can be reliably mapped in non-human mammals.

We believe that our study was an initial step towards identifying the neuroanatomical basis for seizure propagation in patients with laughter as the hallmark seizure semiology. Given the strong lesion overlap in the mammillary level of the hypothalamus, we suggest the following possible candidate nuclei of the hypothalamus in the ictal propagation: (i) mammillary bodies; (ii) histaminergic tuberomammillary nuclei; (iii) the orexin and melanin concentrating hormone positive posterior hypothalamic nuclei; (iv) glutamatergic neurons in the posterior lateral hypothalamus; or (v) the lateral tuberal nucleus (which is a peculiar cell group in the pre-mammillary region in humans that may contain somatostatin and has no clear homologue in rodents). One piece of evidence implicating the orexin neurons in this circuitry is that laughter causes loss of muscle tone in patients with narcolepsy, who lack orexin neurons. Hence, orexin neurons are apparently associated with laughter, and have descending projections that normally prevent the onset of atonia. As orexin neurons also have ascending projections to the amygdala and basal forebrain (Peyron *et al*., 1996, 1998) and are activated by pleasurable stimuli (Harris *et al*., 2005), they may potentiate the laughter, and perhaps gelastic epilepsy.

Future studies can be designed to determine if the hypothalamic hamartomas use the adjacent normal hypothalamic nuclei for propagation of epileptic discharges, or whether they form their own aberrant connections with remote structures. Understanding the neurochemical identity of the hypothalamic hamartoma tissue can help address this remaining question. Staining the pathologic hypothalamic hamartoma samples for orexin, melanin concentrating hormone, histidine decarboxylase (for histamine cells) or *in situ* hybridization for the vesicular glutamate transporter 2 will provide an important first step forward. In future studies of hypothalamic hamartoma specimens obtained from patients undergoing surgery, the pattern of expression of these markers in the hypothalamic hamartoma tissue can be compared with their expression in adjacent hypothalamic nuclei. Future microscopic studies can also determine if the hypothalamic hamartoma tissue is in tandem with the candidate nuclei or whether the hypothalamic hamartoma has the same neurochemical identity as the adjacent nucleus.

Conclusion

One of the aims of the current study was to understand if the hypothalamic hamartomas localize to a particular region of the hypothalamus and the vicinity of any specific hypothalamic nuclei. In line with previous work (Freeman *et al*., 2004), we present overwhelming evidence that lesions causing gelastic seizures are all localized to the mammillary level of the posterior hypothalamus, and that in patients with gelastic events, the longer duration of epilepsy (rather than the location or the size of lesions) determines the development of other seizure types. We are hopeful that these findings will motivate future research towards understanding the precise nuclear anatomy of hypothalamic hamartomas and the routes by which they propagate ictal discharges to cortical and subcortical networks. Such information will help us understand the pathophysiology of epilepsy generated in a subcortical tissue such as the hypothalamus and the routes by which it recruits specific brain networks.

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