Medical management and antiepileptic drugs in hypothalamic hamartoma

J Helen Cross

The Prince of Wales's Chair of Childhood Epilepsy

UCL-Institute of Child Health, Great Ormond Street Hospital for Children< London & Young

Epilepsy, Lingfield, UK

Helen Spoudeas

Consultant in Neuro-Endocrine and Late Effects of Childhood Malignancy

Great Ormond Street Hospital for Children & University College Hospital

Address for correspondence
Professor JH Cross
Clinical Neurosciences
UCL-Institute of Child Health
4/5 Long Yard
London WC1N 3LU
Tel: 44 207 599 4105
Fax 44 207 430 0032
Email: h.cross@ucl.ac.uk

Running title: Medical Management of Hypothalamic Hamartoma

Key words: hypothalamic hamartoma, epilepsy, gelastic seizures, antiepileptic drugs, ketogenic diet

Number of text pages 15
Number of words (summary) 99
Number of words (main text); 2056
Number of tables (main and supplementary); 0
Number of figures 2

Abstract

Hypothalamic hamartoma may present with epilepsy, specifically gelastic or dacrystic seizures, or endocrine dysfunction, commonly precocious puberty. The epilepsy in many is drug resistant, and has a high association with progressive cognitive, learning and behaviour difficulty. Medical treatment of seizures remains problematic, with many resistant to drug treatment. Surgical resection, or disconnection of the hamartoma provides the optimal chance of seizure control but with a realtively high risk of endocrine dysfunction the result of interference with the hypothalamic pituitary axis in many. Careful assessment and monitoring by specialist centres with discussion of optimal intervention is required for individual cases.

Introduction

Hypothalamic hamartoma is a rare but now well recognised pathology causing drug resistant epilepsy, including the pathognomonic gelastic and dacrystic seizures, with marked cognitive and behaviour problems in many. Some however present primarily with precocious puberty, and seizures are not an obvious feature (although they may become evident in retrospect). Medical management is targeted at seizure control and/or delaying or monitoring precocious puberty and growth. In the absence of more conventional seizure types, the biggest challenge remains in diagnosing the seizures, which may remain unrecognised for some time: once diagnosed however, they remain resistant to antiepileptic medications

Making an accurate diagnosis

Accurate diagnosis poses challenges. Patients may be referred in one of two ways – to endocrinologists for investigation of precocious puberty, or alternatively to neurologists for evaluation of epileptic seizures. The pathognomonic seizure type, gelastic seizures, characterized by spontaneous mirthless laughter, often in isolation, are often missed at onset and may remain undiagnosed for some time. Older children and adults do not generally report a feeling of mirth; many report an unpleasant sensation or epigastric discomfort, or indeed a pressure to laugh. In its mildest form, patients may simply report an urge to laugh that can be suppressed. In addition dacrystic, or 'crying' seizures may also be seen but again may go unrecognised. It may only be with the manifestation of more typical epileptic seizures, such as evolution to convulsive seizures, that a diagnosis in retrospect may be made. Although seizures appear the most common presentation to neurology (61%) a significant proportion have (in some unrecognised) precocious puberty at presentation (66%) whilst

25% present with evidence of both[1]. Age at presentation is wide; however early onset gelastic seizures in the first year of life are often missed or misdiagnosed as reflux or colic[2]. Further, a diagnosis of HH may be incorrectly suspected in individuals presenting with focal seizures where laughter is a component of the seizure, arising from the temporal or frontal regions. Also it may be suspected in children with more complex epilepsy with behavour difficulties where laughter may be a manifestation of limited ability in communication. In such cases HH should be excluded with high resolution magnetic resonance imaging but is rarely determined. Where suspected, it must be ensured that an MRI with appropriate sequences has been performed to confirm or eliminate the diagnosis. This would require as a minimum a standard brain MRI protocol with contrast (no enhancement should be seen) including axial coronal T2, axial coronal and saggital T1 and a spin echo post contrast. Further volumetric T1, volumetric FLAIR (or thin T2/Flair sections if not available on scanner) with volumetric sequences reformatted in 3 orthogonal planes (axial,coronal and saggital)[3].

EEG is often normal at the outset, even if documented during a gelastic or dacrystic episode (Figure 1), so such investigational tests do not assist the diagnosis. That aside, EEG is recommended as subtle abnormalities may be apparent. Although not helpful in many with regard to diagnosis, the EEG may change over time[4]. Changes may herald the development of a greater impact in the individual, and consequently an epileptic encephalopathy with increasing cognitive and behavior difficulties. Consequently a sleep EEG may be more revealing than an EEG performed during events. Careful monitoring of the EEG to determine the emergence of abnormalities may aid in decision making with regard to management (see figure 2).

In most patients with HH occurrence is sporadic. However about 5% have HH as part of Pallister Hall syndrome, seen in association with other anomalies such as post axial and central polydactyly, bifid epiglottis and imperforate anus[5], an autosomal dominant condition caused by mutations in the *GLI3* gene[6]. Further recent work has suggested that

the sonic hedgehog (Shh) pathway is intimately involved, but not necessarily limited to a single gene. It appears that somatic mutations probably have an important role. A recently published study demonstrated somatic mutations in genes involving regulation of the Shh pathway in 14/38 individuals (37%) including *GLI3*, but also *PRKACA*, and brain tissue specific large copy number or loss of heterozygosity variants involving multiple Shh genes[7].

Initiation of treatment

The evidence base for the optimal anticonvulsants to use in epilepsy associated with hypothalamic hamartoma, is limited. Most reports comment on medication failure and drug resistance with no particular useful therapy[8]. On assessment at diagnosis of gelastic seizures it is likely a usual protocol for focal seizures will be followed, such as carbamazepine or lamotrigine in the first instance. There is little evidence of response however. Anecdotal evidence suggests zonisamide may be of some benefit. However it also has to be considered that many series are reported from surgical centres and therefore likely to have a bias toward a drug resistant group. There is no question there appears to be a degree of variability in the clinical course, and not all inevitably demonstrate an evolution to marked behaviour and cognitive difficulty, remaining with gelastic seizures alone for many years[9]. In others where precocious puberty has been the prominent presentation, seizures may be entirely absent, diagnosed in retrospect, or where they do occur follow a relatively benign course responding to a variety of different medications[10]. However, individual risk benefit may need to be considered in each case, the aims of treatment being to minimise progression to convulsive seizures rather than reducing gelastic or dacrystic seizures per se, which do not alone appear detrimental to learning. We have no data as to whether medication makes any difference to the natural history of the condition, or on any longer term benefit. In the presence of convulsive

seizures treatment is probably justifed, but in the presence of gelastic or dacrystic seizures alone, the data favouring medical therapy remain limited.

Why are seizures so drug resistant?

The results of EEG recordings from within the hamartoma, and indeed data from surgical series, demonstrate that the epileptic activity originates from within the hamartoma[11;12]. One might speculate that routine anti epileptic medications would poorly penetrate into such a lesion, and hence the poor response of localised gelastic and dacrystic seizures. However, studies of epileptogenesis of tissue from within such lesions suggest that the available antiepileptic agents have a mode of action irrelevant to these lesions. $GABA_A$ receptor mediated activation of L-type calcium channels induce neuronal excitation in excised tissue in vitro[13], and blockade of these channels utilising nifedipine modulates the pathogenic high frequency oscillations in hypothalamic epileptogenic tissue; however this has not yet translated to clinical practice[14] and the role of the newer agents remains untested.

In a significant proportion of children presenting with gelastic seizures, progression is seen over time with the development of other seizure types, increasing cognitive and behaviour difficulties with more evident and/or widespread changes on EEG suggestive of a more widespread encephalopathy. Management should be targeted at preventing such an evolution, with post surgical studies demonstrating a degree of resolution in some cases[15].

The ketogenic diet, a high fat, low carbohydrate, low protein diet, has been used in refractory epilepsy in children for many years. It has been demonstrated to be of benefit in a randomised controlled trial of children with refractory epilepsy of many different types as compared to no change in treatment[16]. It has also been demonstrated to be of particular benefit in children with epilepsy resulting from malformations of cortical development[17]. One publication reports on the use of the ketogenic diet in children with

epilepsy associated with hypothalamic hamartoma; 10/220 children were retrospectively determined to have been treated, with outcome data available in 6. These had been commenced on the diet at a mean age of 12 years, for a median duration of 9 months, although one child who particularly benefitted, continued for 14 years[18]. Four had a 50-90% reduction in multiple seizure types, including gelastic, focal and atonic seizures, and two failed to respond. Possible mechanisms of action were studied utilising microelectrode recordings of small neurons in HH slices; decreased spontaneous firing was seen on exposure to ketone bodies, suggesting a possible benefit in this population.

Beyond the seizures - optimising management

Seizures of course do not present the only aspect of medical management for these children. Many will have subtle, subclinical and undiagnosed endocrine dysfunction, mainly disturbance of growth and puberty, and should be referred for a full dynamic assessment of pituitary function and subsequent longitudinal review even in the absence of overt clinical features.

Hypothalamus-pituitary dysfunction classically includes: a) central premature / precocious activation of the gonadotropin axis and puberty, b) a reduced growth velocity in relation to that child's height trajectory and advanced skeletal and sexual maturation, c) secondary (TSH deficiency) or tertiary (TRH deficiency) hypothyroidism and d) weight gain with eventual obesity and the secondary complications of the metabolic syndrome; f) life threatening ACTH deficiency which would predispose children to addisonian crises, and g) central diabetes insipidus are fortunately rare at presentation. It is however noteworthy that diabetes insipidus almost exclusively occurs in the context of surgical intervention to control seizures, including attempts at hypothalamic disconnection and gamma knife and can, perioperatively, cause severe crises in salt and water balance which in themselves can impair consciousness or aggravate seizures. These data need confirming

in wider data sets which systematically and longitudinally evaluate all children who present with HH from diagnosis, regardless of their presentation (neurological or endocrine) or treatment (medical and/or surgical).

The risk of progressive cognitive and behavioural problems remains high, particularly where there is escalation of seizure frequency and multiple seizure types. Careful neuropsychological assessment, with regular review and educational support/liaison, before and after each major treatment change/intervention, will optimise the input provided to the individual and help determine the benefit or, by contrast, the detrimental contribution of each therapeutic modality to the eventual neuroendocrine outcome. Further behavioural assessment with psychiatric input where required is likely to be of help to families and schools. In such circumstances where behaviour is of concern , there should be early referral for consideration of surgery.

Guidelines on management

A high degree of suspicion is required to ensure appropriate imaging and consequently reach a diagnosis of epilepsy associated with hypothalamic hamartoma. On diagnosis however, although antiepileptic medication should be initiated, referral to a specialist surgical centre should be facilitated so careful followup and appropriate medical/surgical decisions are made. Recognising the lack of response of gelastic/dacrystic seizures to antiepileptic medication, it is not unreasonable to consider holding off medication at this stage. However full endocrine review should be undertaken. Careful regular evaluation should be ensured, including EEG, and, dependent on the type of lesion and clinical manifestation consideration given to early resection or ablation. Antiepileptic medication should certainly be considered with presentation of other seizure types, although the risk benefit of any treatment needs to be considered in individual cases.

What is foreseen in the future?

What is clear on reviewing the literature to date is that many reported observational series have a particular bias according to the centre, especially surgical. In the absence of a comprehensive HH registry of all children, what is difficult to determine is the true prevalence and range of neuro-endocrine presentations, and the overall natural history of the condition with and without intervention, according to radiological features. Of importance is to define which children would benefit from early surgical intervention, and in whom it may be avoided dependent on the risk-benefit ratio. The exceptional rarity of the condition mandates a concerted multicentre and multi professional effort to develop medical protocols for investigation and assessment and a core data set for monitoring neuro developmental and endocrine outcomes in relation to therapy, with pathways in place for early evaluation of appropriate surgical intervention.

Summary

Children (and adults) presenting with epilepsy resulting from hypothalamic hamartoma continue to provide a management challenge. An accurate early diagnosis remains paramount, with recognition of gelastic seizures.. There probably is a role for an initial trial of antiepileptic drugs, selection based on protocols for focal seizures, although more data are required with regard to response, and calcium channel blockers deserve further randomised study. This is particularly relevant if other seizure types emerge. Careful followup and review is required, with monitoring of cognitive function and behaviour and school support, within a specialist unit to ensure optimal timing of consideration of surgical management. Routine endocrine assessment of the hypothalamopituitary axis and

longitudinal review should be part of ongoing medical monitoring, as well as educational and behavioural support.

We confirm we have read the Journal's position on issues involved in ethical publication and affirm that this report consistent with those guidelines

Disclosures

Professor JH Cross has participated in clinical trials for GW Pharma, Zogenix and Vitaflo. She has sat on Advisory Boards and given lectures for Eisai, UCB, Shire and Nutricia. All remuneration has been paid to her department.

Dr HA Spoudeas has participated in clinical study reports for Ferring Pharmaceuticals,for whom she has also sat on Advisory Boards and given lectures with remuneration paid to the department , has been in receipt of unrestricted educational grants from Ferring, Novo Nordisk and SandoZ pharmaceuticals for departmental benefit.

Key points

- Seizures in general resistant to medication
- AEDs used as for focal seizures
- In many treatment targeted at ongoing convulsive seizures rather than gelastic or dacrystic seziures
- Risk of evolution with multiple seizure types, and significant cognitive and behavioural impairment, monitoring
- Many will have at the very least subtle, subclinical and undiagnosed endocrine dysfunction and consequently all warrant review and assessment
- Require early referral for surgical assessment

Figure 1: EEG performed in an 8 year old boy who had onset of gelastic seizures in neonatal period diagnosed in retrospect; generalized tonic clonic seizures onset age 7 years controlled on antiepileptic medication. MRI demonstrated a well defined sessile hypothalamic hamartoma filling much of the third ventricle. EEG monitored during a gelastic event showing no overt change in the recording.

Figure 2: EEG in a 3 year old boy with a history of gelastic seizures since 2 years of age. No other seizure types had emerged, but developmental delay was noted prior to the development of seizures. MRI demonstrates a moderate sized heterogeneous sessile mass centred in the region of the right mamilary body consistent with a hypothalamic hamartoma (C). Sleep EEG recording (A) shows interictal discharges in the left temporal region and frontal polyspikes in sleep. EEG during gelastic events (B) showed diffuse attenuation of EEG activity.

ReferencesReference List

1. Nguyen D, Singh S, Zaatreh M, et al. Hypothalamic hamartomas: seven cases and review of the literature. *Epilepsy Behav* 2003;4:46-258.

2. Nguyen D, Singh S, Zaatreh M et al. Hypothalamic hamartomas: seven cases and review of the literature. *Epilepsy Behav*2003;4:246-58.

3. Parvizi J, Scheherazade Le, Foster BL et al. Gelastic epilepsy and hypothalamic hamartomas: neuroanatomical analysis of brain lesions in 100 patients. *Brain* 2011;134:2960-8.

4. Harvey AS, Freeman JL. Epilepsy in hypothalamic hamartoma: clinical and EEG features. *Semin Pediatr Neurol* 2007;14:60-4.

5. Hall JG, Pallister PD, Clarren SK, et al. Congenital hypothalamic hamartoblastoma,, hypopituitarism, imperforate anus and postaxial polydactyly - a new syndrome? Part I: clinical, causal, and pathogenetic considerations. *Am J Med Genet* 1980;7:47-74.

6. Kang S, Graham JM, Jr., Olney AH, et al. GLi3 frameshift mutations cause autosomal dominant Pallister-Hall syndrome. *Nat Genet* 1997;15:266-8.

7. Hildebrand Ms, Griffin NG, Damiano JA, et al. Mutations of the Sonic Hedgehog Pathway Underlie Hypothalamic Hamartoma with Gelastic Epilepsy. *Am J Hum Genet* 2016;99:1-7.

8. Arzimanoglou A, Hirsch E, Aicardi J. Hypothalamic hamartoma and epilepsy in children: illustrative cases of possible evolutions. *Epileptic Dis* 2003;5:187-99.

9. Arzimanoglou A, Hirsch E, Aicardi J. Hypothalamic hamartoma and epilepsy in children: illustrative cases of possible evolutions. *Epileptic Dis* 2003;5:187-99.

10. Cukier P, Castro LHM, Banaskiwitz N et al. The benign spectrum of hypothalamic hamartomas: infrequent epilepsy and normal cognition in patients presenting with central precocious puberty. *Seizure* 2013;22:28-2.

11. Specchio N, Rizzi M, Trivisano M et al. Acute intralesional recording in hypothalamic hamartoma: description of 4 cases. *Acta Neurol Belg* 2014;Oct 10 [Epub ahead of print].

12. 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.

13. Kim YO, Fenoglio KA, Simeone TA et al. $GABA_A$ receptor-mediated activation of L-type calcium channels induces neuronal excitation in surgically resected human hypothalamic hamartomas. *Epilepsia* 2008;49:861-71.

14. Simeone K, Sabesan S, Kim DY, Kerrigan JF, Rho JM, Simeone TA. L-typpe calcium channel blockade reduces network activity in human epileptic hypothalamic hamartoma tissue. *Epilepsia* 2011;52:531-40.

15. Freeman JL, Harvey AS, Rosenfeld JV, Wrennall JA, Bailey CA, Berkovic SF. Generalized epilepsy in hypothalamic hamartoma: evolution and postoperative resolution. *Neurology* 2003;60:762-7.

16. Neal EG, Chaffe HM, Schwartz RH et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol* 2008;7:500-6.

17. Jung DE, Kang HC, Kim HD. Long-Term outcome of the Ketogenic Diet for Intractable Childhood Epilepsy with Focal Cortical Malformation of Cortical Development. *Pediatrics* 2008;122:e330-e333.

18. Chapman KF, Kim DY, Rho JM, Ng NT, Kerrigan JF. Ketogenic diet in the treatment of seziures associated with hypothalamic hamartomas. *Epilepsy Res* 2011;94:218-21.