

# Hypothalamic hamartoma in adults

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**ABSTRACT** – Epilepsy in adult patients with hypothalamic hamartoma has not been well studied. It is uncommon but merits recognition. In this paper, 14 adult patients with hypothalamic hamartoma and epilepsy, of whom three developed epilepsy only in adult life, are presented. The later onset of epilepsy appears to be associated with a milder epilepsy syndrome, less severe learning difficulties and behaviour problems, and better occupational and social status. Gelastic seizures are less prominent in this age group. Of particular interest, one patient had prominent sleep disturbances characterized by a reduction in total slow wave and REM sleep without daytime sleepiness.

The milder epilepsy and preserved cognitive and social functioning have implications for management. A number of patients were controlled by anticonvulsant medication, and were functioning satisfactorily. For such patients minimally invasive surgical procedures, or medical therapy should be considered.

**KEY WORDS:** hypothalamic hamartoma, epilepsy, gelastic seizures.

Hypothalamic hamartoma (HH) is often associated with a catastrophic epilepsy syndrome associated with gelastic seizures and refractory epilepsy. Sometimes, precocious puberty (PP), behaviour problems and learning difficulties occur [1]. While most of the literature on the subject describes the clinical manifestations and treatment in children, there are recent reports of adult patients with HH [2]. Generally, the manifestations of HH in adults are poorly understood, since it is regarded as very rare. However, with improvements in neuroimaging, it is inevitable that a greater number of adults with HH, some without the typical manifestations, will be detected. Recently we have had the opportunity to evaluate a number of such patients with HH, and we present our experience below.

## Patient details

Fourteen adult patients were evaluated at King's College Hospital between 1999-2002. Some of them are part of a larger group of patients, both

children and adults with HH who have been evaluated at our centre, and the details of which have been published elsewhere [7]. All patients were evaluated with a detailed history and examination, MRI scans, EEGs, video EEG (in five patients) and neuropsychological assessment (six patients). Their ages ranged from 16-56 years (mean 33.5 years). Seven were female. All patients presented clinically with refractory epilepsy. Only one patient presented with gelastic seizures, although, on reviewing the seizure details, overt gelastic seizures were present in six patients. In a further four patients, the gelastic nature of the seizures existed only as mere feelings of "a need to laugh", and in another patient, although gelastic seizures had been present in childhood, they had subsequently stopped completely. Three patients never had gelastic seizures. Two of these patients developed epilepsy in adult life, and the third developed epilepsy at the age of 13, after presenting with precocious puberty at the age of 7 years.

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Eleven patients had epilepsy that began in childhood, but all of these patients had been diagnosed as having HH only in adult life. In three other patients with HH, the epilepsy only began in adult life. Presenting seizure types were tonic seizures (n = 5), complex partial seizures (n = 8), and atonic seizures (n = 4). Atypical absences were particularly frequent in one patient. Two patients had moderate learning difficulties, and six had mild learning difficulties. Seven of these adult HH patients were in employment and six were married or in long term relationships. A history of precocious puberty, although borderline, was present in two other patients.

Two cases are illustrated below.

### Case 1

This 35 year-old man works full time. Although only diagnosed as having HH at the age of 30 years, his symptoms probably began as a baby when it was noted that he had attacks of inappropriate laughter. These subsided, only to recur at the age of six, but they were not troublesome and were not recognized as seizures. Early development was normal, and he went to normal school, passed his secondary school examinations, and was able to obtain a qualification in carpentry. More overt seizures with giggling and confusion, and generalised tonic clonic seizures, began in his teens but they did not significantly hamper his education. Subsequently, he held down a number of jobs and is presently working in a factory. He is married and has two children.

He currently has seizures which begin with a nervous giggle, of which he is aware, and which is not associated with mirth. This progresses to swallowing and sometimes, oral and limb automatisms develop. On occasions, more complex automatisms develop, such as walking on to the road and directing traffic. During these episodes, he speaks irrelevant but clear sentences. He has post-ictal confusion lasting up to 30 min. Frequency of complex partial seizures reduced on treatment with tiagabine and carbamazepine. His main seizure type now comprises brief gelastic attacks which occur several times a week. MRI scans show a 1cm diameter HH in the third ventricle above the mamillary bodies. EEGs show bilateral temporal sharp waves. Neuropsychological evaluation shows a full scale IQ of 108, with a verbal IQ of 96 and a performance IQ of 123, moderate impairment of verbal short term memory and intact visuospatial memory.

### Case 2

This 33 year-old musician presented with a two year history of infrequent, abrupt falls to the ground and episodes of blankness. The attacks of falling occurred without warning and, on occasions, he has injured himself. Falls were

followed by a brief period of unresponsiveness occurring once every few months, but tonic clonic jerks have never been noted. The episodes of blankness were brief and occurred in clusters, resulting in days when he was not able to do much, and these occurred once every few weeks. He was treated with lamotrigine, with some benefit. He is able to work full-time, as the front manager of a theatre and has a long-term girlfriend. His early development was normal, and he went to normal school. On review, it became apparent that puberty probably was precocious and began around the age of eight years. His partner abnormal interictal sleeping pattern. As far as he can remember, he has never slept much. He normally goes to bed between 11 pm and midnight and will take about an hour to fall asleep. He will then wake two or three times in the night, toss and turn and then get up to watch television or do some work. He then returns to sleep and awakens around 7 am. He is not "a morning person", but does not feel sleepy during the day. This has been his normal sleep pattern all his life. He reports that on occasions when he does fall asleep, he has very vivid dreams, which he can recall on awakening. Sometimes he has hypnagogic hallucinations. He has never had sleep paralysis, nor does he have irresistible urges to sleep in the daytime. He is not troubled by his sleep pattern and is surprised that other people seem to sleep 7-8 hours every night.

The MRI scan revealed a small, 4 mm diameter HH arising from the left mammillary body. An EEG showed occasional temporal sharp transients. Video EEG telemetry performed over five days with reduction of lamotrigine, showed no interictal abnormalities and there were no attacks of blankness or falling. On the 3<sup>rd</sup> and 4<sup>th</sup> night of this study, polysomnography was performed. On both nights, it was confirmed that the patient slept very little, between four to five hours in bed, with frequent arousals every few minutes. Total sleep time was about three and a half hours. The maximum period of stage two/three sleep was one and a half hours: he had little slow wave sleep and no REM sleep.

### Discussion

The epilepsy syndrome noted in adult patients with HH appears to be different from the catastrophic epilepsy noted in children, and this is particularly the case when the epilepsy begins in later life. The differences are highlighted below.

#### Differences between adults and children with hypothalamic hamartoma

##### Milder epilepsy with later onset

Our findings suggest that the later onset of epilepsy in patients with HH is associated with a milder epilepsy

syndrome. The epilepsy syndrome is usually restricted to one or two partial seizure types, commonly complex partial ("pseudotemporal") seizures, or tonic seizures, with a variable expression of gelastic seizures, and occasional generalized seizures. This is different from children with early onset epilepsy, which begins with gelastic and other partial seizures at the onset and progresses to multiple refractory seizure types and, on occasions, symptomatic generalized epilepsy develops [1, 2].

### **Gelastic seizures are less prominent with later onset of epilepsy**

Gelastic seizures appear to occur less frequently when the epilepsy begins later in life. All three patients with HH who did not have gelastic seizures had developed epilepsy later in life, after the age of 10 in one patient, and in two others, at the age of 26 and 31 respectively. When the epilepsy begins early in association with HH, gelastic seizures almost always occur. Eleven of our patients with HH had the onset of epilepsy before five years of age, and all had gelastic seizures. Gelastic seizures became either less prominent and were reduced to "mere feelings of an urge to laugh" or completely disappeared as the patient entered into teenage and adult life, in five of our 14 patients. Sturm *et al.* [1] who describe it as "pressure to laugh", have also reported this feature in two adult patients with HH and mild epilepsy.

### **Learning difficulties are less common**

Thirdly, the later onset of the epilepsy (and the absence of the symptomatic generalized epilepsy) appears to be associated with significantly fewer learning difficulties. Half of the patients in this series were in employment and all, except two patients who were in residential care, were independent in Activities of Daily Living but living with family members. This is in contrast to the early onset epilepsy in children with HH, where up to two thirds had moderate or severe learning difficulties [5]. Deonna and Ziegler reviewed the literature for documented cases of HH with normal cognition [6]. Of 67 cases in the literature with details of cognition and behavior, 10 were reported to be of normal intelligence. Six of these involved late onset (one patient with adult onset), but four patients had early onset epilepsy, similar to our patient described above as case 1. At the present time, there are no definitive data to indicate exactly how epileptic pathology interferes with development, cognition and behaviour in HH. Suggested mechanisms are excitotoxic damage to the mamillary bodies and the medial thalamus from the frequent epileptiform discharges from the HH [7]. It is also postulated that frequent epileptic discharges in the hypothalamic amygdala and frontal systems at an early developmental age interfere with the processing of life experiences and result in aberrant personality or behavioural changes [6]. Six of our patients with HH who have a normal IQ have

been shown, on neuropsychological testing, to have specific and disproportionate memory deficits.

### **Behaviour problems are fewer with later onset**

Finally, behavioural problems occur in children with HH. Weissenberger *et al.* reported on 12 children with HH and gelastic seizures [8]. When compared to their unaffected siblings, children with HH had a statistically higher rate of psychiatric conditions, including oppositional defiant disorder (83%), attention deficit/hyperactivity disorder (75%), aggression (89%), conduct disorder (33%), speech retardation/learning impairment (33%), and anxiety and mood disorders (17%). In another study, Fratelli *et al.* reported on eight children, six of whom had rage attacks with kicking, screaming and biting behaviour [9]. The same six also had poor relationships with peers, characterized by tendencies towards self-isolation and self-directed play. The adults in our series have not been formally psychiatrically tested, since they do not have any significant psychiatric symptoms. No history of aggressive and defiant behaviour in childhood was noted. However, they all appeared to be loners, with poor peer relationships. The majority of the adults ( $n = 10$ ) were introverted, placid, shy individuals. Two were rather disinhibited and chatty individuals. Two patients in residential care also appeared rather placid, except when seizures occurred.

### **Sleep problems in HH**

Von Economo studied the brains of people affected by encephalitis lethargica, a presumed viral illness which causes profound sleepiness. He noted the relationship between lesions of the posterior hypothalamus and profound sleepiness [10]. He also recognised patients with the opposite problem i.e. those patients who had a prolonged state of insomnia and had a lesion of the preoptic area and basal forebrain. It is now established that sleep active neurons occur in the preoptic area (POA) of the hypothalamus and the basal forebrain, and sleep results because of the increased activity of these neurons. The posterior hypothalamus, which facilitates the awake state, contains hypocretin neurons. The different stages of sleep occur as a consequence of the interaction between different monoaminergic nuclei, the POA and the pedunculo-pontine, lateral tegmental nuclei. REM sleep occurs due to increased firing of the extended venterolateral POA nuclei (VLPOA) [11, 12]. It is possible that in our patient, described above as Case 2, the HH has produced an impairment of function of the POA and VLPOA nuclei. Severe epilepsy, frequent antiepileptic discharges and behavioural problems have usually complicated the evaluation of sleep in patients with HH. The patient described above is of normal intelligence, having infrequent seizures and gave a clear account of his sleep difficulties. The absence of REM sleep was striking on the hypnogram, on

the two nights studied. In addition, there were very frequent arousals, and reduction of slow wave sleep. Most strikingly, the lack of night-time sleep was not associated with any day-time sleepiness: this patient's overall sleep clock and sleep requirements appeared to have been altered. Although the scalp EEG showed no abnormality during the polysomnography, a possible explanation for the sleep problems would be that the frequent HH discharges, unrecordable on the surface EEG, disturb the function of the POA/ PPT, LDT systems.

Dunn *et al.* evaluated 6 patients with HH and gelastic seizures, and refractory epilepsy, and noted sleep difficulties, and in particular, a reduction in REM sleep in patients with HH [13]. The reduction in REM sleep was related to the severity of the seizures. They have therefore suggested that the reduction in REM sleep contributed to the increased severity of seizures. Our impression is that increased seizures and epileptiform discharges from the HH interfere with generation of REM and slow wave sleep, or that both effects operate in a circular fashion, each exacerbating the other.

### Management aspects - medical or minimally invasive

All of the 14 adult patients are receiving treatment with AEDs. Two of the patients have considerable learning difficulties and may not be able to make a fully informed decision about surgical therapy. Two other adults have had stereotactic thermocoagulation, with significant benefit to their seizures and no side effects. Ten other patients, of whom seven are in employment, are reasonably satisfied with the AED treatment and do not wish to consider surgery. Indeed, given their high level of functioning, it would be difficult to justify a surgical procedure which carries the risk of a considerable degree of morbidity. For such patients, we believe that either minimally invasive procedures, such as stereotactic thermocoagulation should be performed, or the best possible epilepsy control achieved with AEDs. In patients with symptomatic, generalized EEG discharges, broad spectrum AEDs appear to confer additional benefit. □

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