[Review: 2 table; 2 figures; 3 supplementary tables; 1 supplementary figure]

Neuropsychiatric profile of paediatric hypothalamic hamartoma: systematic review and case series

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[Abstract]

AIM To evaluate neuropsychiatric comorbidities in children and adolescents with hypothalamic hamartoma.

METHOD We retrospectively analysed case notes for all individuals with hypothalamic hamartoma referred to Great Ormond Street Hospital, London, between 2000 and 2016. In addition, a systematic review aiming to identify all previous paediatric case series was performed. Psychiatric symptoms, demographics, physical comorbidities, and cognitive functioning were recorded for all cases where possible. Analyses were performed to determine which factors were associated with psychopathology and potential mechanisms investigated.

RESULTS Forty-six cases were included in the case series (28 males, 18 females; mean age at assessment 11y 8mo (1y 11mo to 16y 11mo, SD 4y 0mo). Twenty-nine papers representing data from 264 cases met inclusion criteria for the systematic review. Overall, at least 50% of cases presented with psychopathology. Epilepsy, intellectual disability, and male sex were associated with externalizing disorders (attention-deficit/hyperactivity disorder, conduct and oppositional defiance disorders, and rage attacks). Intellectual

disability mediated the effects of epilepsy on externalizing psychopathology. No factors were associated with internalizing disorders (anxiety and depressive disorders), although these were not well reported.

INTERPRETATION Psychiatric comorbidities are highly prevalent in the presentation of paediatric hypothalamic hamartoma. The aetiology of psychopathology comprises a range of interacting biological and psychosocial factors with particular influence from epilepsy. Further research is required to achieve an evidence base for treatment.

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[Boxed text to appear on page 2]

What this study adds

- Over half of children with hypothalamic hamartoma present with psychiatric comorbidity.
- Externalizing and internalizing disorders are present in approximately 60% and 30% of children with hypothalamic hamartomas respectively.
- Epilepsy and male sex are associated with externalizing psychopathology.

- Intellectual disability mediates the association between epilepsy and externalizing symptoms.
- No clear associations are evident for internalizing disorders or precocious puberty.

[Main text]

HYPOTHALAMIC HAMARTOMAS

Hypothalamic hamartomas are rare, congenital, benign tumours arising from the hypothalamus. The estimated incidence is one per 50 000 to 100 000.[1] They typically occur sporadically although some genetic syndromes (most notably Pallister–Hall syndrome) have been shown to predispose individuals to their development.[2,3] Sporadic cases are proposed to result from somatic mutations leading to the abnormal regulation of early hypothalamic development. Genotyping of surgically resected hypothalamic hamartoma tissue has demonstrated mutations in sonic hedgehog pathway genes in up to 40% of sporadic cases, a quarter of which share the germ-line abnormality *GLI3* gene found in Pallister–Hall syndrome.[4]

Affected individuals present with a clinical syndrome of seizures and/or central precocious puberty, alongside a range of neuropsychiatric manifestations. Anatomical classification systems for hypothalamic hamartomas vary, but the distinction of intrahypothalamic versus parahypothalamic has been proposed to correlate well with clinical presentation.[5] Intrahypothalamic lesions cause more disruption to the hypothalamus and hence give rise to epileptic and psychiatric symptoms of greater severity.[6] The epileptic profiles for children with hypothalamic hamartomas are often characterized by an onset of gelastic seizures (which resemble attacks of mirthless laughter) before progression towards other seizure types which may be focal and/or generalized. Typical seizure onset varies from early presentation in the first days of life to late presentation in adolescence or early adulthood.[7] The seizures are markedly drug-resistant.[8] Parahypothalamic tumours (which attach to the anterior

hypothalamus in the region of the tuber cinereum and pituitary stalk) are more commonly associated with central precocious puberty. This is the presenting feature in around two-thirds of individuals.[9] A further complexity is that an estimated 40% of patients have symptoms of both refractory epilepsy and precocious puberty due to large hypothalamic hamartoma lesions which attach anteriorly and posteriorly.[10] Additionally, determining the endocrinological impact on the neuropsychiatric profile of hypothalamic hamartomas is complicated by the fact that rates of occult growth hormone deficiency (the most frequent anterior pituitary hormone deficiency in the context of any hypothalamic injury)[11] are unknown. This is of relevance given the deficiency's documented associations with a variety of neuropsychological deficits.[12]

Psychiatric manifestations of hypothalamic hamartomas

The psychiatric manifestations of hypothalamic hamartomas are varied and frequently present the greatest burden of morbidity for families. They are likely to result from a complex pathoaetiology involving interacting neurobiological and psychosocial factors. Research into the psychopathology of hypothalamic hamartomas has been largely limited to descriptions in case reports and case series owing to the rarity of the disorder. For this reason, reported prevalence rates are variable, but recent estimates indicate that up to 50% of cases present with progressive comorbid cognitive impairment and psychiatric symptomatology.[13] Longitudinal relationships and possible causal pathways between the physical phenotypes (epilepsy and precocious puberty), psychiatric phenotypes, and cognitive profiles of children with hypothalamic hamartomas have not been fully established.

Cognitive impairment

The cognitive profiles of children with hypothalamic hamartomas vary from normal to severe intellectual disability; additionally, cognitive dysfunction may be progressive. Factors

associated with more severe cognitive impairment include larger tumours, early seizure onset, higher seizure frequency, and use of multiple antiepileptic medications.[13] These findings are largely consistent with findings in other hamartomatous disorders such as tuberous sclerosis.[14]

Externalizing symptoms

Externalizing disorders involving disruptive or aggressive behaviour are commonly reported in hypothalamic hamartomas.[9,15,16] Patients often meet diagnostic criteria for attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder.[15,16] A characteristic component is the presence of 'rage attacks'. These explosive episodes are thought to be both secondary to poor frustration tolerance and a result of affective (as opposed to predatory) aggression.[15]

The presentation of aggressive behaviour is consistent with the role the hypothalamus plays as a mediator of rage. Patients subjected to posterior hypothalamotomies for hyper-aggression in an era when psychosurgery was deemed more acceptable showed significant reduction in symptoms.[17] Conversely, other reports suggest that the rage exhibited in hypothalamic hamartomas is more in keeping with 'multifactorial bouts of challenging behaviour seen with mental retardation'[18] rather than the classical sham rage of hypothalamic lesions. The literature also highlights evidence of children presenting with autism spectrum disorder and/or autistic traits,[19] further adding to the hypothesis of the aggression being in part a result of generic challenging behaviour. There is also the likelihood that precocious puberty/possible growth hormone deficiency may both contribute to the presentation of behavioural problems[12] but this has not been well investigated.

Internalizing symptoms

Internalizing disorders including anxiety (generalized anxiety, phobias, obsessive–compulsive disorder, tics) and affective dysfunction have also been described in hypothalamic hamartomas.[16,20] A direct contribution of the hypothalamus in the pathophysiology of internalizing disorders has previously been illustrated; abnormalities in the corticotrophin-releasing hormone pathway within the hypothalamic pituitary axis have been shown to predispose children to anxiety and depression. [21] However, these disorders also present at high prevalence rates in young people suffering from epilepsy and precocious puberty without direct hypothalamic dysfunction.[22–26]

It is of interest that the psychiatric phenotypes seem distinct from other in vivo presentations of 'classical' hypothalamic dysfunction (which are more apparently related to disruption of the hypothalamic nuclei responsible for homeostasis of the organism). For example, the hypersomnia and extreme hyperphagia seen in Prader–Willi syndrome (proposed to be a result of abnormal oxytocin signalling in the hypothalamic paraventricular nucleus)[27] and eating disorders seen in hypothalamic germinoma and pinealoma[28] have not been well described in children with hypothalamic hamartomas. It is possible that the physical phenotype(s) in hypothalamic hamartomas are more relevant than direct hypothalamic dysfunction in explaining the neuropsychiatric sequelae.

Psychosocial factors

Alongside the significant neurobiological impact, psychosocial factors contribute towards the psychiatric phenotype in young people with hypothalamic hamartomas. A standardized analysis of the quality of life in children with hypothalamic hamartomas has indicated significant reductions across all domains of the assessment tool (in categories of physical, emotional, social, and school functioning) than those observed in a comparison group with migraine.[29]

AIMS AND HYPOTHESES

This study reports a large collection of paediatric cases of hypothalamic hamartoma from a single tertiary referral centre. It aims to assess whether the symptom profile of this cohort is similar to previous descriptions in other settings. To do this, we systematically reviewed the literature for all past case series of hypothalamic hamartomas describing psychiatric presentations in children and adolescents. In so doing, a subsequent aim was to elucidate prevalence rates of paediatric psychiatric symptoms and diagnoses more thoroughly than has been done previously.

A further intention was to investigate potential risk factors for psychopathology. The main study questions were therefore the following. (1) Does epilepsy associate with the presence of psychiatric symptoms? (2) Does central precocious puberty associate with the presence of psychiatric symptoms? (3) If associations are found, can these be explained by mediating or moderating factors?

A priori hypotheses were that epilepsy and intellectual disability would be associated with externalizing symptoms, while precocious puberty would be associated with internalizing psychopathology.

METHOD

Case series

All patients with hypothalamic hamartomas referred to Great Ormond Street Hospital, London, between 2000 and 2016 were included in the case series. Forty-six children met criteria for inclusion. All case notes from outpatient specialist clinics (including psychiatry/psychology/neurology/neurosurgery and endocrinology) and relevant inpatient stays were reviewed. Clinical records were analysed to ascertain demographics,

neuropsychiatric symptom profiles, epileptic profiles, use of antiepileptic medications, and pubertal status. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) was used to define the presence of a psychiatric disorder. The manual describes the necessary symptom(s) required to make diagnoses of clinical psychiatric disorders.[30] Diagnoses were assigned where this had been done previously by specialists, or where symptom descriptions in the documentation were sufficient to meet ICD-10 diagnostic thresholds. Aside from 'rage', symptoms that did not make clinical diagnostic threshold for a disorder were not recorded. Degrees of cognitive dysfunction were assigned on the basis of documented formal cognitive assessments, or case reports according to reported Full-scale IQ criteria of mild (50–69), moderate (35–49), or severe (20–34) or unspecified as to type. Central precocious puberty was defined in females by onset of breast stage 2 before 8 years and in males as testicular volume greater than 4ml by 9 years and/or needing treatment with a gonadotropin-releasing hormone antagonist.

Systematic review

A systematic review was conducted by two independent researchers in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. S1, online supporting information). Three databases were searched: PsycINFO (1974 to 6th February 2019), MEDLINE (1970 to 6th February 2019), and Embase (1970 to 6th February 2019). Full texts were searched for the terms: (child* OR adolescen* OR paediatric* OR pediatric*) AND (hypothalamic hamartoma* OR hypothalamic hamartoblastoma*) AND (behavio* OR psych* OR cognitive*). Reference lists of relevant studies and reviews were hand-checked for additional references.

Inclusion criteria were as follows: (1) articles describing an assessment of psychiatric symptoms/diagnoses and/or cognitive profiles in children and adolescents (up to an age of 19y

inclusive) with an MRI diagnosis of hypothalamic hamartomas; (2) articles reporting on case series of a minimum of three cases; (3) English language publications.

The following information was extracted from articles meeting inclusion criteria: article characteristics (i.e. whether primarily assessing surgical outcomes or providing a stand-alone description of symptoms), geographical location, demographics (age at assessment, sex), physical comorbidities (neurological and endocrine), psychiatric comorbidities (symptoms/diagnoses reported, reported method of assessment), level of cognitive function (formal and informal reports), and follow-up time. Data for individual patients were extracted where possible. Where it was clear that all cases in the series met inclusion criteria, reported mean values were used. Cases that had clearly been duplicated between papers (determined through assessing duplicated demographic/clinical data and by contacting the author[s] where relevant) were included only once in the analysis. Owing to the range of reporting styles by authors, where cases within the series were reported to have a presence of a symptom/diagnosis, the remaining cases were recorded as having a specific absence of that symptom/diagnosis. If the symptom/diagnosis was not mentioned at all within the paper, the cases were recorded as having missing data pertaining to that symptom/diagnosis. Proportions reported therefore exclude cases in which these data were missing.

Statistical analysis

Analyses of the Great Ormond Street Hospital data and the review data were undertaken separately. Mann–Whitney *U* tests (for continuous variables) and χ^2 tests (for categorical variables) were performed to test for group differences between participants with and without the presence of externalizing/internalizing symptoms.

Using the data from the systematic review, the relation between epilepsy and the presence of externalizing symptoms was tested to investigate whether this was mediated by the

presence of intellectual disability. We performed mediation analysis using the non-parametric bootstrap method (1000 samples).[31]

Statistical analyses for the case series and review used the statistical programming language R (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria). A mediation model using the R package 'Mediation' (version 4.4.6) with quasi-Bayesian Monte Carlo simulation (10 000 simulations) tested for significance.[32] The 'ggplot2' package (version 2.2.1) was used for figure construction. Statistical significance was set throughout at *p*-values less than 0.05, two-tailed.

RESULTS

Case series

Neuropsychiatric profiles

The cohort consisted of 46 children (28 males, 18 females) diagnosed with hypothalamic hamartomas. The mean age at diagnosis was 2 years 5 months (1mo to 15y 0mo, SD 3y 8mo). Mean age at assessment by psychiatry/psychology was 11 years 8 months (1y 11mo to 16y 11mo, SD 4y 0mo).

A total of 65.2% of cases experienced seizures, with a mean age at onset of 2 years 11 months (SD 2y 10mo). The most common seizure type experienced was gelastic (in 97% of those with epilepsy), followed by generalized tonic–clonic (41.4%) and partial/complex partial (37.9%). In those diagnosed with epilepsy, seizure frequency was high, with a mean of approximately 11 seizures per day (SD 13.8). The mean number of antiepileptic medications trialled in these children was three (SD 1.5).

Seventy per cent of children met criteria for at least one axis 1 ICD-10 disorder. The proportions of cases presenting with individual disorders/symptoms are indicated in Figure 1. Sixty-one per cent presented with evidence of externalizing symptoms, with 45% of the whole

cohort exhibiting rage attacks. Twenty-eight per cent presented with internalizing symptoms. Fifteen per cent had evidence of an autistic spectrum disorder; 58.5% displayed evidence of intellectual disability; 17.4% of those with intellectual disability had the severe subtype. Fifty-four per cent of all cases had been reviewed by child psychiatry or psychology either within the tertiary centre or at local secondary care centres.

Neuropsychiatric dysfunction and associated features

Tables I and SI (online supporting information) show associations with several possible clinical and demographic risk factors for externalizing and internalizing symptoms. Externalizing symptoms were significantly more common in individuals with an epilepsy diagnosis (χ^2=9.04, degrees of freedom [df]=1, p=0.002), and in those with moderate and severe intellectual disability (vs mild or no intellectual disability) (χ^2=7.1, df=1, p=0.007). Male patients and those diagnosed at a younger age were more likely to have an externalizing disorder, but not at the level of significance.

Internalizing symptoms showed no significant associations with any of the measured clinico-demographic factors (p>0.05 for sex, epilepsy, and intellectual disability).

Precocious puberty and associated features

Precocious puberty was present in 40% of cases. No associations were evident with internalizing (χ^2=1.55, df=1, p=0.22) or externalizing (χ^2=0.37, df=1, p=0.55) symptoms.

Systematic review

From the original search, 371 papers were identified, with a further three from hand-searching of reference lists. After full screening and exclusion, 29 papers met final inclusion criteria. See Figure S1 for the PRISMA diagram.

Study characteristics

Table SII (online supporting information) describes characteristic features of the included case series selected for the systematic review. The case series contained between 3 and 29 cases. Two hundred and sixty-four cases were identified in total, of which 65.1% were males. The mean age at assessment was 9 years 5 months (1mo to 19y 0mo, SD 5y 5mo).

Fifteen of the cases series were primarily concerned with the evaluation of surgical techniques. Eleven case series provided descriptive records of patients' symptoms, three of which investigated correlations between radiographic/anatomical findings and symptomatology,[5,33,34] and three of which described the cognitive profiles of patients.[35–37] Only three case series used validated diagnostic instruments for assigning neuropsychiatric diagnoses.[15,16,38] In two case series, parental reports were used.[15,35] Most reports did not provide any details as to how diagnoses were established or describe performance of a non-specific 'neuropsychological assessment' for cases.

Neuropsychiatric profiles

A total of 89.3% of cases were reported to have seizures. The mean age at onset was 1 year 6 months (SD 2y 5mo). Among all cases, gelastic seizures were most common (88.1%), followed by partial or complex partial (40.1%), and generalized tonic–clonic (30.1%). Other seizure types were reported in 46.6%. The most common number of seizure types presented was two (39.0%), with three and four seizure types presenting in 23.7% and 7.6% respectively. Central precocious puberty was reported in 39.6% of cases.

There was evidence of a psychiatric disorder in 60.3% of cases. Figure 1 illustrates the proportions of children presenting with each psychiatric disorder or symptom description. Evidence of an externalizing disorder presented in 55.7% of cases, with 40.6% of the whole

cohort exhibiting rage attacks. Evidence of an internalizing disorder presented in 31.1% of cases and 18.3% presented with an autistic spectrum disorder. Reporting of disorders was highly heterogeneous between series, with significantly more emphasis paid to describing externalizing symptoms and less report of the specific absence of disorders/symptoms.

Cognitive dysfunction was described in 57.1% of cases. The precise subtype of intellectual disability was not well reported, with almost a quarter of cases being unspecified as to type. From the remaining cases, mild intellectual disability was more common (22.0%) than moderate (3.8%) or severe (16.4%) types.

Neuropsychiatric dysfunction and associated features

Tables II and SIII (online supporting information) show clinical risk factors associated with externalizing and internalizing disorders for the included cases. In keeping with the findings of the case series, the presence of seizures was strongly associated with the presence of an externalizing disorder (χ^2=12.1, df=1, p<0.001). Male patients were significantly more likely to show externalizing disorders (χ^2=16.2, df=1, p<0.001). The presence of intellectual disability was also significantly associated with the presence of an externalizing disorder (χ^2=13.9, df=1, p<0.001) and rage attacks (χ^2=8.0, df=1, p=0.005).

Bivariate analyses did not identify any significant associations between the presence of internalizing disorders and any clinico-demographic factor (p>0.05 for male sex, epilepsy, seizure burden, and intellectual disability).

Precocious puberty and associated features

Precocious puberty was associated with increased anxiety (χ^2=7.5, df=1, p=0.006), but had no association with an overall diagnosis of an internalizing (χ^2=2.5, df=1, p=0.11) or externalizing (χ^2=2.9, df=1, p=0.09) disorder.

Mediation analysis

On bivariate analysis in logistic regression modelling, intellectual disability and epilepsy were both predictors for the presentation of externalizing symptoms. Results of the logistic mediation analysis are shown in Figure 2. The significant direct pathways between epilepsy and intellectual disability (β=0.62, 95% confidence interval [CI] 0.27–0.98), and intellectual disability and externalizing disorder presentation (β=0.25, 95% CI 0.12–0.39), are demonstrated. The pathway from epilepsy to externalizing disorder presentation became non-significant once mediation through intellectual disability was taken into account (β=0.32, 95% CI −0.02 to 0.64, p=0.08 vs β=0.17, 95% CI −0.15 to 0.57, p=0.3). Indirect mediation pathway through intellectual disability was also significant (β=0.14, 95% CI 0.04–0.21, p<0.001), indicating that intellectual disability was a full mediator within this model.

DISCUSSION

This study has found associations between several risk factors and a range of psychopathological disorders in children and adolescents with hypothalamic hamartoma. Although other studies have looked at the risk for isolated behavioural traits,[13] this is the first, to our knowledge, to attempt to rigorously determine the prevalence rates and associated risk factors for this range of disorders. The case series presented here (the largest so far reported for paediatric hypothalamic hamartomas) and systematic review both demonstrate that hypothalamic hamartomas in children and adolescents are associated with a significant burden of neuropsychiatric morbidity. Reviewing data from 264 cases indicates that up to 90% have a diagnosis of epilepsy, around 60% present with intellectual disability, and over 50% have significant psychiatric symptoms. Externalizing disorders predominate but there is also a significant burden of internalizing psychopathology. A comorbid diagnosis of epilepsy is

strongly associated with externalizing psychopathology. Male sex and cognitive dysfunction also seem to associate with externalizing symptoms. Furthermore, it seems that intellectual disability may act as a mediator for the effects of epilepsy on the presentation of externalizing symptoms. There were no associations detected with the proposed potential risk factors for internalizing psychopathology from this data. Additionally, psychiatric symptoms did not seem to be associated with precocious puberty.

It is noteworthy that these associations are more similar to children with other complex epilepsies[22,23] rather than primary hypothalamic disorders. A meta-analysis of children with epilepsy showed similar findings in that externalizing symptoms, particularly attentional problems, were associated with seizures.[39] Furthermore, the behavioural phenotype in hypothalamic hamartomas is strikingly similar to that found in tuberous sclerosis, another disorder in which the developing brain is affected by refractory seizures. A causative pathway from a high burden of seizures towards intellectual disability has been illustrated[24] and this pathway is proposed to extend towards explaining a large component of the subsequent behavioural difficulties. Mechanistically, seizure activity seems to affect aspects of working memory and attention, creating both a cognitive deficit and a 'neuropsychological vulnerability' to behavioural problems.[40] In addition to the direct neurotoxic effects that an epileptic encephalopathy arising from uncontrolled epilepsy produces, the same children are more likely to experience the adverse behavioural side effects from polypharmacy related to multiple antiepileptic medications.

Internalizing disorders are evident at similar rates in hypothalamic hamartomas to those of young people with epilepsy. The prevalence rate of 30% in the current study is, however, considerably lower than the rates of 80% for depression, and anxiety and depression, in adult patients with hypothalamic hamartomas.[20] It is possible that this discrepancy is accounted for by the fact that the mean age at assessment presented here is pre-adolescent and development

of these symptoms mirrors the presentation in those without hypothalamic hamartomas, occurring mainly in mid–late adolescence. An alternative explanation is poor detection and/or reporting of symptoms through limited involvement of psychiatric services. It is not clear from the literature how many children with hypothalamic hamartomas worldwide are being seen in psychiatric services; however, the lack of clarity about how psychiatric symptoms were detected in the review studies suggests that these children might not be accessing psychiatric support.

Although most probably having some impact, the contribution of direct hypothalamic dysfunction towards psychopathology was not specifically tested in this study. The reported low prevalence of eating and sleeping disorders, as replicated in the wider literature, indicates that the input from a disordered hypothalamus is of less aetiological importance. Furthermore, the lack of association between psychiatric symptoms and precocious puberty suggests that hormonal dysregulation in these patients is also less of a biological contributory factor.

Psychosocial factors also have a significant contribution towards the psychiatric phenotype in young people with hypothalamic hamartomas. Common to many children with chronic physical diseases, impairments in self-esteem, poor coping skills, and poor self-concept have been demonstrated.[29] The numerous and varied clinical symptoms in children with hypothalamic hamartomas are likely to exacerbate these concerns. Aggression, attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder all show associations with the aforementioned psychological concerns. In addition, the possible under-recognition of anxiety and depression because of emphasis on physical health issues may lead to inadequate treatment and further deterioration. Subsequent increased aggressive behaviour may be a possible sequela. This may set the stage for a negative feedback loop with deterioration in physical health secondary to non-compliance with treatment.

Despite the high burden of psychiatric and cognitive disability experienced by children with hypothalamic hamartomas, efforts towards formal characterization of the presentation(s), use of validated assessment tools, and discussion around appropriate psychological or pharmacological treatments have been limited. This systematic review indicates that focus has been principally on non-specifically describing features (with an aim of evaluating interventional procedures) without reference to diagnostic frameworks. Exploratory studies comparing psychopathology in children and adolescents with hypothalamic hamartomas to sibling controls,[15] and investigation into predictive factors for aggression,[13] have aimed to rebalance this shortfall of targeted investigation and understanding. This study presents a further step towards determining the prevalence rates of particular disorders and supports improved emphasis on prospective and systematic assessment to inform intervention strategies.

Strengths and limitations

This is the first study, to our knowledge, aimed at determining the prevalence of paediatric hypothalamic hamartomas psychopathology (through pooling of international case series) and specifically characterizing associated factors. A systematic approach to this task is presented using a large case series and review of other case series within the literature. The main limitation of the study is the scarcity of quality reporting about the methods of assessment for the disorders. Very few articles contained any reference to the use of any standardized tools used to reach a diagnostic category. In most cases, the ambiguous term of 'neuropsychological assessment' was used without reference to who undertook these assessments. This makes the findings biased towards inaccurate representation of disorders, and most probably under-representation of internalizing disorders. Second, the lack of longitudinal data in some studies may lead to an under-representation of symptoms, further reducing the likelihood of detection of internalizing psychopathology because of a pre-adolescent mean age at assessment, without

later follow-up data. From an endocrine perspective, rates of central precocious puberty are also likely to be an underestimation as many patients were not seen by endocrinology services. Furthermore, the neuropsychiatric impact from delaying puberty using gonadotropin-releasing hormone antagonists is unknown as it was not specifically ascertained which patients were receiving these medications.

Where it was evident that cases were described twice in different articles, these individuals were only included once in the analysis. However, where this was unclear (and secondary to pooling of international cases) there is a risk that crossover between case series may have occurred with some patients.

Publication bias also presents a limitation. Most of these case series were published with the intention of evaluating surgical or other procedures. Therefore, children who were not considered for intervention are under-represented in these case series. Similarly, children presenting to endocrine clinics with well-controlled or without comorbid epilepsy are not represented well in the series. Furthermore, authors whose papers did not report descriptions of symptoms were not contacted to supply any outstanding data that may have been missing.

The method of using retrospective case-note review for detecting psychopathology in the case series is also less favourable for an accurate representation of symptoms than a prospective operationalized in-person assessment. Additionally, the decision to use the diagnostic framework of the ICD-10 to assign diagnoses is a further limitation given that current classification schemes are limited in their ability to accurately map phenotype to underlying neurobiology. Although attempts are being made to develop dimensional biologically informed classification schemes, these are not currently suitable for use in the case of retrospective diagnosis. A further limitation is illustrated by the fact that some risk factor associations in the review were not replicated in the Great Ormond Street Hospital series. This

is most likely due to the small sample size of the series, meaning that it was underpowered to detect these associations.

Future considerations

This study highlights that neuropsychiatric symptoms are extremely common in young people with hypothalamic hamartomas. It is unclear whether the need for appropriate assessment and treatment of these symptoms is currently met. The increased use of standardized tools in clinical practice would allow more accurate characterization of neuropsychiatric symptomatology. Furthermore, attempts to diagnose psychiatric disorders more formally may address the need for greater recognition of possible internalizing disorders. Future research may also explore whether similarities exist between hypothalamic rage attacks and tantrums seen in other children with intellectual disability.

Although clearly a challenging task, it is possible that effective early seizure control may have an impact on reducing subsequent cognitive and behavioural difficulties. This is currently being undertaken in tuberous sclerosis, with randomized controlled trials for molecular therapies aimed at reducing neuropsychiatric symptoms.[41]

There are significant moves towards investigating the impact of surgical interventions on psychiatric and cognitive symptoms in hypothalamic hamartomas. Although this is clearly a valuable area of research, it may at times eclipse efforts to manage cases with behavioural and pharmacological strategies. It is interesting to note that a 2-year follow-up for children after epilepsy surgery in patients with complex seizures showed higher rates of psychiatric illness from baseline.[42] This emphasizes further the necessity of finding non-surgical ways of managing these multifaceted problems.

Conclusion

Young people with hypothalamic hamartomas have a high prevalence of psychopathology. Despite this, there is a dissonance between burden of morbidity and international attempts to formalize the detection and management of psychiatric disorders. A comorbid diagnosis of refractory epilepsy and intellectual disability further increases the likelihood of presenting with externalizing psychopathology. The hormonal impact of puberty and other possible endocrine deficiencies on the psychiatric presentation requires further study. Owing to the rarity of the disorder, international collaboration will undoubtedly be required to achieve an evidence base for non-surgical treatments of this rare and complex disease.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table SI: Factors associated with presence/absence of an internalizing disorder: Great Ormond Street Hospital case series

Table SII: Studies included in the systematic review

Table SIII: Factors associated with presence/absence of an internalising disorder: systematic review studies

Figure S1: PRISMA 2009 flow diagram.

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Table I: Factors associated with presence/absence of an externalizing disorder: Great Ormond Street Hospital case series

	Presence of externalizing disorder	Absence of externalizing disorder	Odds ratio	*p*
Males, % (*n*/*N*)	64 (18/28)	56 (10/18)	1.4	0.55
Epilepsy, % (*n*/*N*)	82 (23/28)	39 (7/18)	6.9	0.002[a]
Mean age (SD) at epilepsy diagnosis (y:mo)	2:6 (2:10)	3:11 (2:11)	—	0.22
Mean number (SD) of antiepileptic medications	3.8 (1.5)	3.2 (1.6)	—	0.35
Mean seizure frequency (SD) (average number/d)	9 (10)	18 (22)	—	0.27
Central precocious puberty, % (*n*/*N*)	54 (15/28)	44 (8/18)	1.4	0.55
Intellectual disability, % (*n*/*N*)	68 (17/25)	47 (8/17)	2.3	0.17

[a]Statistically significant associations ($p<0.05$).

Table II: Factors associated with presence/absence of an externalizing disorder: systematic review studies

	Presence of externalizing disorder	Absence of externalizing disorder	Odds ratio	*p*
Males, % (*n*/*N*)	79 (99/125)	54 (49/91)	3.2	<0.001[a]
Epilepsy, % (*n*/*N*)	98 (123/126)	84 (85/101)	7.7	<0.001[a]
Mean age (SD) at epilepsy diagnosis (y:mo)	1:7 (2:6)	1:11 (2:7)	—	0.31
Central precocious puberty, % (*n*/*N*)	30 (35/115)	42 (41/97)	0.6	0.05
Intellectual disability, % (*n*/*N*)	70 (86/123)	45 (38/85)	2.9	<0.001[a]

[a]Statistically significant associations ($p<0.05$).

Figure 1: Proportions of cases presenting with psychiatric disorders/symptoms in Great Ormond Street Hospital (GOSH) case series and systematic review studies. ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; CD, conduct disorder; ODD, oppositional defiant disorder; OCD, obsessive–compulsive disorder.

Figure 2: Mediation path diagram. Path diagram of the multiple mediation model of the effect of epilepsy on externalizing disorder through intellectual disability. The model displays standardized beta coefficients of the direct effects of epilepsy and intellectual disability on externalizing disorder; and the indirect effects of epilepsy on externalizing disorder through intellectual disability. Beta coefficients with significant effects (p<0.05) are shown in bold with solid lines. The lower arrow refers to the unadjusted bivariate relation between epilepsy and externalizing disorders (the italicized coefficients relate to the direct effect once the mediating effect of intellectual disability has been taken into consideration).

Figure 3: T2 sagittal MR image showing hyperintense lesion consistent with hypothalamic hamartoma arising from the left hypothalamus and filling the third ventricle.