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Hypothalamic hamartoma: epilepsy and neurodevelopmental profiles in a clinical cohort

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ABSTRACT

Objective. We aimed to determine the prevalence of epilepsy and neurodevelopmental disorders, including autism spectrum disorder, in children and adolescents with hypothalamic hamartoma (HH). We also sought to explore the relationship between these neurodevelopmental comorbidities and epilepsy and to establish the predictive value of structural characteristics of the hamartoma itself.

Methods. We retrospectively studied a cohort of 62 children with HH, with neuroimaging reviewed at Great Ormond Street Hospital (GOSH) between 2008 and 2018. Clinical records were reviewed, cognitive and language data analysed, and MRI scans studied.

Results. We confirmed a high burden of epilepsy (56%), autism (19%) and other neurodevelopmental disorders. Although rates of some neurodevelopmental disorders were significantly higher in those with epilepsy, autistic features and/or early developmental concerns often predated the onset of seizures, in particular generalized seizures, or occurred independently of seizures. We found a significant correlation between certain structural characteristics of the hamartoma itself and both epilepsy and certain neurodevelopmental comorbidities.

Significance. These findings suggest that although seizure burden clearly contributes to the cognitive and behavioural phenotypes seen, the hamartoma itself, and particular characteristics of it, are likely to be primary determinants of both the epilepsy and neurodevelopmental profiles. It is also probable that the underlying aetiology, likely genetic, directly contributes to the clinical profile, with epilepsy, neurodevelopmental impairment and the hamartoma itself representing markers of this aetiology. We propose that atypical neurodevelopmental profiles in HH could best be conceptualized as a developmental and epileptic encephalopathy. These findings have implications for counselling, monitoring and treatment.

Key words: hypothalamic hamartoma, epilepsy, neurodevelopmental disorders, autism, paediatric

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Hypothalamic hamartomas are rare non-neoplastic malformations, composed of hyperplastic neural tissue, which vary in size, attachment and effects on surrounding tissues. They are usually sporadic but some genetic syndromes predispose to their development, *e.g.* Pallister-Hall syndrome. Their association with epilepsy, central precocious puberty (CPP) and cognitive

dysfunction is well recognized. In addition, a high rate of neuropsychiatric diagnoses has been reported, including behavioural and attentional difficulties [1-4]. Autism has not been as clearly described.

Cognitive dysfunction in children with HH has previously been attributed to epilepsy. Berkovic *et al*. described progressive deterioration of cognition and behaviour, in parallel with evolution of epilepsy, in a longitudinal study of four patients, and suggested that cognitive decline is attributable to worsening epilepsy [5]. Deonna and Ziegler, in a case study and literature review, reported a temporal link between cognitive deterioration and epilepsy, concluding that the cognitive dysfunction represents a direct effect of the seizures [6].

A more complicated relationship has been suggested by others, whereby structural factors, seizure severity and frequency, age at seizure onset, and medication interact to influence cognitive status [4, 7-11].

Previously published research has been limited by small cohorts, exclusion of patients of lower abilities and surgical bias. These limitations, in addition to variety in comorbidities described, have made direct comparisons difficult and led to inconsistent findings and conclusions across studies, including disagreement about the direct effect of seizures.

The primary aim of this study was to determine prevalence rates of epilepsy and neurodevelopmental comorbidities, including autism, and to investigate the relationship between the two, in a large cohort of children with HH from a single quaternary referral centre. The impetus was our observation that autistic features and early developmental impairments appear to predate the onset of seizures in some HH patients, prompting the question *"Are subtle differences in neurodevelopmental profile evident prior to seizure onset in more children than previously suspected?"* We considered the possibility that this entity could be better understood as a developmental and epileptic encephalopathy.

A secondary aim was to identify structural predictors of particular clinical profiles. Anatomical classification systems have allowed the relationship between structural characteristics of HH and clinical presentation to be explored [12, 13]. Nevertheless, there is a lack of consensus regarding the predictive value of structural characteristics of HH [4, 8, 9, 11-15].

In short, we questioned the suggestion that the neurodevelopmental associations of HH are simply the direct consequence of seizure activity. We also sought to clarify the predictive value of certain structural characteristics of HH, with clinical surveillance in mind.

Materials and methods

Patient selection

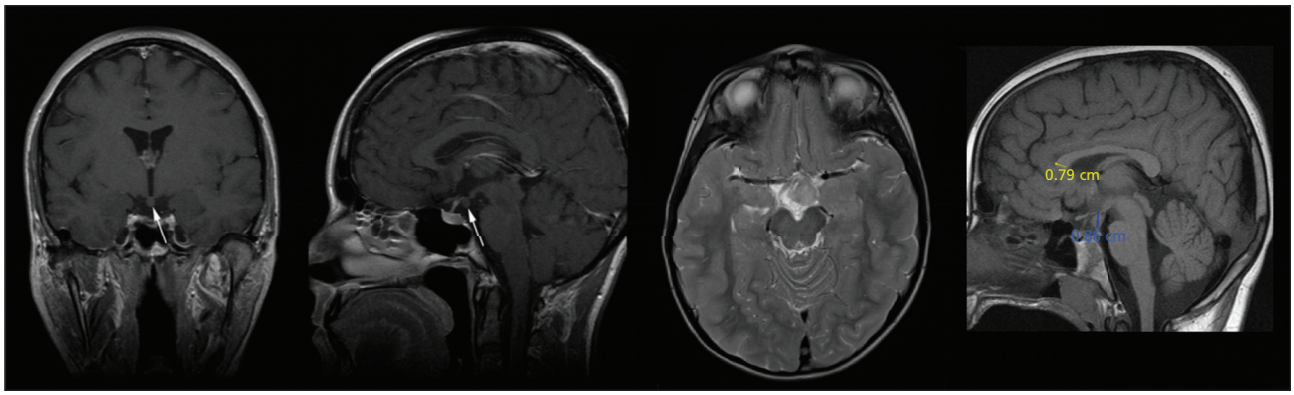
In order to identify all HH patients with MRI brain scans reviewed at GOSH, our imaging database was interrogated, from May 2008 to April 2018, using the search term "hamartoma". This search yielded 736 reports, 89 with definite or possible HH. No images were found for seven cases. The available scans (82) were reviewed by a paediatric neuroradiologist and the cohort was refined. Twelve cases were excluded because HH was not confirmed, and an additional eight were subsequently omitted because of insufficient clinical information, leaving a cohort of 62.

Clinical and radiological data

Clinical and neuroimaging data were collected, including age at first presentation and age at last review, and are summarized in *supplementary table 1*. Clinical records on our electronic clinical document database were carefully reviewed, for all cases, including outpatient specialist clinic letters and inpatient discharge summaries. Information gathered included demographics, presentation, seizure history, developmental diagnoses and concerns and CPP. Available cognitive and language data was double rated and analysed to determine the developmental profiles.

MRI scans were rated by the same paediatric neuroradiologist. Three structural parameters of the HH were assessed. First, we measured size. HHs are non-progressive but expand with brain growth; consequently, their relative size remains the same [16]. Therefore, we expressed size as a relative value, a ratio of HH size to corpus callosal size. We used the first available MRI scan in our PACS system for each patient, not always corresponding to the age at diagnosis. We measured the maximum cranio-caudal diameter of the HH on sagittal T1 WI (solid part in case of cystic-solid HH). We used as, internal reference, the genu of the corpus callosum, using a method of linear measurement, as described by Garel *et al*. [17] and shown in *figure 1*. Normal values, provided by Garel, allowed us to confirm normal callosal size in all of our patients. We defined large size as a HH:genu ratio >1.5.

Second, attachment type was classified as either sessile, if it had a broad-based attachment, or pedunculated, if attached to the tuber cinereum without displacement of the hypothalamus [12]. MR images demonstrating attachment types are displayed in *figure 1*. Finally, the relationship to the mammillary



■ **Figure 1.** Coronal (A) and sagittal (B) post-contrast T1-weighted images (WI) showing a pedunculated hypothalamic hamartoma (HH). C) Axial T2-WI showing a sessile HH. D) Sagittal image showing an example of the measurements of HH and genu of the corpus callosum.

bodies was evaluated, as an indicator of the impact of the HH on surrounding structures.

Statistical analysis

Statistical analysis was performed, with the support of the GOSH Digital Research Environment team and Aridhia system, to determine which structural factors were associated with epilepsy, through binomial logistic regression analysis and neurodevelopmental comorbidities and the significance of epilepsy for each neurodevelopmental diagnosis by chi square analysis.

Definitions

Based on this information, we categorized children by clinical diagnosis, including intellectual disability (ID), language disorder and autism. We also included broader categories of cognitive, social communication, attentional and behavioural concerns, which included children with formal diagnoses as well as those for whom results of assessment and standardized questionnaires were significantly indicative of difficulties in these areas.

We stipulated a definite clinical diagnosis of autism, based on Diagnostic and Statistical Manual of Mental Disorders (DSM) IV or V criteria. Given that ID is a clinical diagnosis, we specified ID as Full Scale Intellectual Quotient (FSIQ) or cognitive indicator less than 70, on formal testing. We elected to include those with an uneven cognitive profile on formal testing (cognitive skills below 80 in some areas but not all). Language scores less than 70 or an uneven language profile, on standardized assessment, defined language impairment. "Global developmental delay", a clinical diagnosis in DSM-V, was defined as impaired early development in two or more domains, including motor and language, based on clinical history from the first three years of life.

Results

Cohort characteristics

There were roughly equal numbers of male (32) and female (30) patients in our cohort. The commonest presenting complaint was seizures, in 39% (24/62), followed by CPP in 32% (20/62). Of those presenting with CPP, 20% (4/20) subsequently developed epilepsy. HH was discovered incidentally in six cases. The commonest clinical profile was that of epilepsy only in 39% (24/62), followed by CPP only in 29% (18/62). Eighteen percent (11/62) of the cohort had both CPP and epilepsy.

Epilepsy profile

In total, 56% (35/62) of our cohort had epilepsy. A higher proportion of those with autism had epilepsy, namely 83% (10/12), but their epilepsy profile was similar.

Multiple seizure types were seen, often in combination. Most commonly documented were gelastic seizures, the signature seizure type, in 88% (31/35) of those with epilepsy. Dacrystic seizures were recorded much less frequently, in only 14% (5/35). Generalized tonic-clonic seizures (GTCS) were seen

in 49% (17/35) of cases with epilepsy. Focal seizures, seen in 54% (19/35), often had temporal lobe semiology. Drop attacks were not uncommon, seen in 20% (7/35), and spasms were seen in 8% (3/35).
First documented seizures were gelastic in 57% (20/35) of children with epilepsy and were first recognised between birth and four years of age; seven cases had onset in early infancy. GTCS had a broader age of onset, emerging between five months and 18 years of age.
Seizures began early in the majority of those with epilepsy, at less than two years of age in 69% (24/35) and less than one year in 57% (20/35). Whereas first seizures, often gelastic, began on average at 10 months, generalized seizures began years later, on average at 70 months.

Neurodevelopmental morbidity

Because we were using historical, retrospective data, full developmental data was not always available. Some may have been unable to complete formal assessment, due to behavioural difficulties or limited abilities regarding certain measures, but many were not referred due to lack of concern, focus on epilepsy management or, in the past, because the service had not yet been developed. Current practice includes referral for neurodevelopmental assessment.
We found a high rate of neurodevelopmental comorbidity in this group. Nineteen percent (12/62) of the cohort had autism, and social communication concerns were identified, on standardized questionnaires, in 34% (21/62). Thirty one percent (19/62) had ID and 42% (26/62) had cognitive impairment, defined more broadly. Twenty one percent (13/62) had language impairment, based on formal assessment. Behaviour concerns were documented in 39% (24/62) and attention concerns in 31% (19/62).
Formal neurodevelopmental assessment data was available in 43.5% of children (27/62). Children were referred for a developmental assessment when there was a reported concern about development or surgical intervention was considered.

- ***Cognitive profiles***

Twenty-six cognitive assessments were completed (age range: 7-197 months; mean: 114.44; SD: 62.05). Of these, six had cognitive scores within the average range. Six of the score profiles were uneven and 14 children had a score within the ID range. The child who did not complete a cognitive assessment, due to seizure activity and attention difficulties, had a clinical diagnosis of ID. These results are summarised in *table 1*.

- ***Language profiles***

Formal language assessment was completed in 29% (18/62) (age range: 7-197 months; mean: 92.25; SD: 60.66). Of these, five had average language profiles, three had a mixed profile, and 10 had a language impairment ranging from mild to severe; eight severe, one moderate, and one mild. Of the children with severe difficulties, four had assessments in which only age equivalences could be calculated.
Of those with language impairment, 33% (9/13) had a diagnosis of autism. The distribution of the results of language assessment is shown in *table 1*.

- ***Combined language and cognitive assessments***

Seventeen children had both language and cognitive assessments; 13 on the same day. Of these 17 children, two demonstrated both language and cognition in the average range. Five had discrepant profiles, with language disproportionately affected, and 10 demonstrated language and cognition in the language impairment and ID range, respectively. One child completed a language assessment, which revealed language impairment; this child did not complete cognitive assessment but had a known ID diagnosis.

- ***Behaviour and attention***

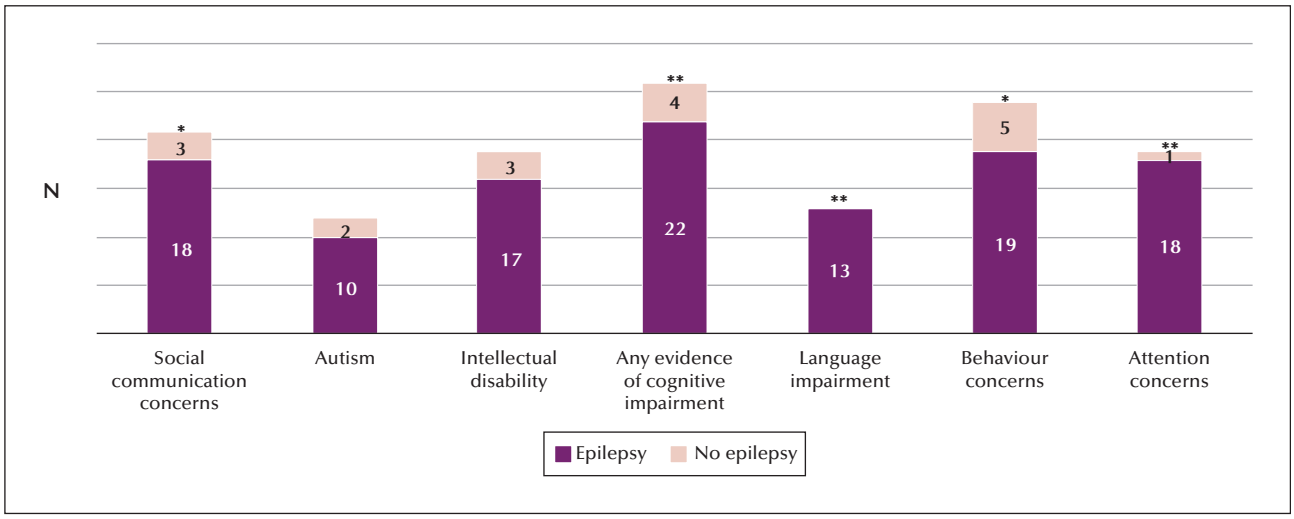
The majority of the sample referred for neurodevelopmental assessment had behaviour (17/27) and attention difficulties (16/27).

- ***Neurodevelopmental profile and epilepsy***

We considered the relationship between neurodevelopmental morbidity and epilepsy and found significantly higher rates of neurodevelopmental disorders in those with epilepsy, with the exception of autism

▼ **Table 1.** Distribution of results of cognitive and language assessment.

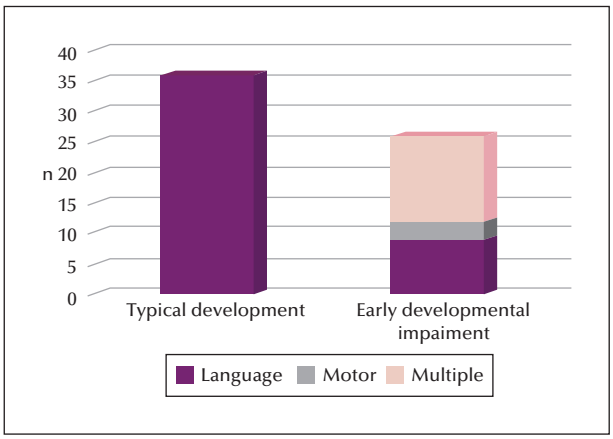
N (%)	Cognitive skills	Language skills
ID/language impairment	14 (54%)	10 (56%)
Uneven profile of skills	6 (23%)	3 (17%)
Skills within average range	6 (23%)	5 (28%)



■ **Figure 2.** Neurodevelopmental profiles: relationship with the presence or absence of epilepsy. The significance of epilepsy was calculated for each diagnosis using Pearson chi-square (*p<0.05, **p<0.01).

and ID. *Figure 2* demonstrates the significance of epilepsy for each diagnosis.
Reduction in seizure frequency or resolution of seizures, in 53% (8/15), following surgical intervention, was associated with improved development in only one case and, unexpectedly, deterioration in behaviour in another.

• ***Global developmental delay***
Early developmental information was available in approximately half of the cohort (26/62). If not documented in clinical records, it was considered likely that no developmental concerns had been raised and that development could be presumed to be typical. Even if this assumption led to underestimation of early developmental concerns, we found a very high rate of developmental impairment, which was unrelated to the presence of epilepsy; 42% (11/26) did not have epilepsy. Of the whole cohort, 14.5% (9/62) had delayed language acquisition in isolation, 4.8% (3/62) had delayed motor milestones in isolation, and 22.5% (14/62) had impairment in two or more domains, consistent with global developmental delay.
Figure 3 illustrates the distribution of impairments and the number with typical development (36/62).



■ **Figure 3.** Early development: number of cases with typical development and distribution of early developmental impairments as percent of the cohort.

• ***Reported onset of autistic behaviours compared to seizure onset***
On review of early developmental history, in those with a formal diagnosis of autism, autistic features were found to have antedated the onset of any reported seizures, or occurred in the absence of seizures, in 50% (6/12). Autistic behaviours antedated onset of generalized seizures in 75% (9/12).
Table 2 summarises the relationship between onset of social communication concerns and seizure onset in children diagnosed with autism.

Structural predictors of epilepsy and neurodevelopmental morbidity

Mammillary body involvement was found to be a statistically significant predictor of epilepsy and ID. There was also a significant correlation between

▼ **Table 2.** Onset of autistic behaviours compared to seizure onset.

	Any seizure	Generalised seizure
Same time	2	0
Before	4	9
After	6	3

Children with autism without reported seizures are included.

sessile attachment type and epilepsy. However, we found no significant correlation between large size and autism, ID or epilepsy. Mammillary body involvement, sessile attachment and large size combined were highly predictive of epilepsy and ID (*table 3*).
Of those with pedunculated attachment type, 30% (7/23) had epilepsy in our cohort. It is also noteworthy that none of our cases had associated epileptogenic lesions, such as malformations of cortical development, despite focal seizures in 54%.

Discussion

Cohort characteristics

The commonest presenting complaints in our series were seizures (39%) and CPP (32%).

Whilst Cukier concluded that where CPP is the prominent presentation, seizures may be absent, diagnosed in retrospect, or follow a relatively benign course [18], we discovered that presentation with CPP by no means excluded the possibility of epilepsy, seen in 20%. This finding has important implications for counselling of families.
One possible explanation for the older mean age at diagnosis for seizures, than for CPP, could be the subtle nature of some gelastic and dacrystic seizures and the often normal EEG at the outset, even during a seizure [19].

Epilepsy profile

In total, 56% of our cohort had epilepsy. High prevalences, up to 90%, have been reported previously [1].

▼ **Table 3.** Structural predictors of epilepsy, autism and ID.

		Est	Std error	Z value	*p*	
Epilepsy	>1.5 ratio	0.2628	0.6804	0.386	0.69927	
	Mammillary body	2.6397	0.8916	2.961	0.00307	**
	Sessile	1.3806	0.6667	2.071	0.03839	*
	All	-2.7062	0.8745	-3.095	0.00197	**
Autism	>1.5 ratio	-0.3023	0.6768	-0.447	0.655	
	Mammillary body	17.6280	1578.8603	0.011	0.991	
	Sessile	0.1067	0.7748	0.138	0.890	
	All	-18.5558	1578.8603	-0.012	0.991	
ID	>1.5 ratio	-0.2580	0.6057	-0.426	0.67010	
	Mammillary body	2.4739	1.1259	2.197	0.02800	*
	Sessile	0.9573	0.6829	1.402	0.16099	
	All	-3.1791	1.1117	-2.860	0.00424	**

Significance of structural characteristics calculated for each diagnosis with Pearson chi-square (*p<0.05, **p<0.01).

Seizures were usually of early onset in our cohort, less than two years in 70%. First seizures, often gelastic, began earlier (average: 10 months) than generalized seizures (average: 70 months). These findings are comparable to Freeman's discovery that generalized tonic seizures began years later than gelastic seizures [15]. The discrepancy between age at onset of gelastic and generalized seizures is not surprising, given that gelastic seizures are most likely to originate in the intrinsically epileptogenic hamartoma itself [20], whereas generalized seizures are postulated to be attributable to secondary epileptogenesis, possibly due to the intimate relationship between the HH and the mammillothalamic tract [15].

Other seizure types were documented in our series, most notably focal seizures (54%) but also spasms and drop attacks. Others have reported spasms [15]. Extensive interconnections between the HH and cortical and other networks could explain the emergence of other types of seizures [14, 15]. Thus, consideration of HH should not be confined to children presenting with the signature seizure type.

Neurodevelopmental profile

- ***Autism***

A significant proportion of our cohort had a diagnosis of autism (19%) and an even larger proportion had social communication difficulties (34%). An autism prevalence of 15% has previously been reported [1]. A higher proportion of patients with autism had epilepsy (83%), albeit with a similar epilepsy profile. This is not surprising, given the known high prevalence of epilepsy (8-20%) in children with autism generally [21].

Autistic features often antedated the onset of seizures, or occurred in the absence of seizures, in those with autism; any seizures in 50% and generalized seizures in 75%. When seizures did appear to predate the onset of autistic features, the seizures were of very early onset, such that one could not exclude the possibility of co-existing social communication concerns at that time.

These findings suggest that autism in children with HH is not directly attributable to seizures and/or an epileptic encephalopathy, as previously suggested [5, 6]. Rather, they support the notion of a neurobehavioural clinical profile due to the HH itself, and its rich interconnections, and/or the underlying aetiology, likely genetic.

- ***Cognition***

Undoubtedly, the prevalence of ID (31%) was underestimated, given that many children could not complete formal neuropsychological testing. Others have noted that there are many children, with significant cognitive and behavioural problems, who are "not testable" and that these children are often excluded from important analyses [2, 14]. We felt it was important to include these children in the analysis, however, which is why we created the category "cognitive impairment more broadly defined" (42%).

- ***Language impairment***

A language disorder was confirmed in 21% of our cases. However, it should be noted that only one third of the cohort were formally assessed. The association with autism (9/13) is not surprising, given that some element of language disorder is usually a key feature of autism. However, four cases did not have autism, consistent with the suggestion that the HH itself may have potential to interrupt typical language development [14, 15]. Alternatively, or in addition, disordered language may be indicative of widespread effects of the underlying pathogenesis.

An interesting finding was that language and cognitive profiles were discrepant in five of those who had both assessments. Our understanding is that language and cognition usually develop along the same trajectory in those with global developmental impairment. Our discovery that language seems to be disproportionately affected in some suggests that there may be more specific disruptions to development in these children.

- ***Global developmental delay***

The high rate of early developmental impairment in our cohort, whether or not epilepsy was present, provides more evidence that there is something intrinsic to the hamartoma itself that is interrupting typical brain development. Prigatano *et al*. noted that children with HH, with or without CPP, may show unequivocal developmental abnormalities that predate the onset of seizures [4].

As children with early developmental impairment generally do not "catch up", unlike those with isolated delays, we would predict that this would be the case for HH patients with impairment in multiple domains, although this study did not allow confirmation of this.

- ***Neurodevelopmental profile and epilepsy***

In our series, a number of neurodevelopmental comorbidities were significantly more likely to occur if epilepsy was present, in particular cognitive impairment (more broadly defined), attentional difficulties, social communication concerns, language disorder and behavioural concerns. Others have reported a strong association between epilepsy and externalising psychopathology, such as attention deficit hyperactivity disorder and aggressive behaviour, in children with HH [1]. Thus, the presence of epilepsy does influence the neurodevelopmental

profile. However, this relationship is not clearly causative; both may represent markers of the underlying brain pathophysiology.
Improvement in development in only one of eight cases, with reduction or resolution of seizures following surgery, suggests a multifactorial pathogenesis for neurodevelopmental dysfunction, as proposed by others [4, 7-11]. Deterioration in behaviour in another, despite reduction in seizures, may have been due to antiepileptic drug (AED) withdrawal and/or forced normalization. Thus, even when surgery improved seizure control, other parameters were often not affected.

Structural predictors of epilepsy and neurodevelopmental morbidity

Large size in combination with mammillary body involvement and sessile attachment type was highly predictive of epilepsy and ID in our series. Large size alone was not significantly predictive for epilepsy, autism or ID in our series. This finding concurs with some previous reports [8]. However, others have found a negative correlation between size and cognitive performance [4, 9].
We found a significant correlation between mammillary body involvement and both epilepsy and ID and between sessile attachment type and epilepsy. Sessile attachment was associated with refractory seizures, with or without cognitive and behavioural abnormalities, in several series [12, 13, 15]. Conversely, Striano *et al*. reported no cognitive or behavioural disturbances in six patients with sessile HH [11]; it is noteworthy that the hamartomas in this series were all small.
In our series, pedunculated attachment type did not preclude epilepsy, which was seen in 30%. Valdueza *et al*., however, concluded that pedunculated hamartomas are likely to be asymptomatic or associated with CPP alone [12].
Although there is a lack of consensus in the literature regarding the predictive value of structural characteristics of HH, our findings suggest strongly that mammillary body involvement and sessile attachment are useful predictors of epilepsy and ID, particularly in combination with large size.

Conclusions

Our findings strongly suggest that whilst seizures have the potential to contribute to cognitive and behavioural dysfunction, the hamartoma itself is likely to be a primary determinant of the neurodevelopmental and epilepsy profiles. This could be explained by its capacity to progressively disturb surrounding structures and networks, thereby interrupting typical brain development, in a similar way to a congenital tumour [4, 15, 22, 23].
We postulate that the underlying aetiology, likely genetic, directly contributes to the clinical profile, the hamartoma, epilepsy and neurodevelopmental impairments representing markers of this aetiology. Indeed, somatic mutations in sonic hedgehog (Shh) pathway genes have been demonstrated, in surgically resected tissue, in up to 40% of sporadic cases, including the *GLI3* gene known to be associated with Pallister-Hall syndrome, suggesting that impaired Shh signalling is one pathogenic pathway of HH [24, 25].
We conclude that the hamartoma itself and underlying genetic factors directly influence the neurodevelopmental and epilepsy profiles, whilst seizures can contribute to cognitive and behavioural dysfunction. Thus, the clinical phenotype associated with HH might best be conceptualized as a developmental and epileptic encephalopathy.
Our findings have implications for clinical practice. First, the clearly demonstrated developmental vulnerability of these children dictates close monitoring. Second, structural characteristics, and presence or absence of epilepsy, can be used to predict the clinical course, allowing an individual approach to counselling, planning of follow up, and consideration for early surgery [15, 26].

Challenges

This study has several limitations. First, many children could not complete formal neuropsychological testing. Second, it could be challenging to use longitudinal data in a meaningful way, as assessments, diagnostic criteria and terminology changed and awareness of comorbidities and their importance increased. In addition, there may have been a bias towards more severe cases, as a result of the quaternary status of our hospital.
Finally, our study shares the limitations associated with all retrospective studies. First, there were inevitable gaps in the data, which was based on available clinical records. Second, rates of epilepsy and neurodevelopmental disorders were likely to be underestimates, as some children were relatively young at last review and those without epilepsy may not have been monitored as closely. In addition, dynamic profiles were not accounted for and the timing of assessments was not uniform. Finally, confounding factors for cognitive and behavioural function, including endocrine factors, effects of AED therapy, and seizure frequency and severity, were not accounted for.
A strength of the study is that it includes one of the largest single-centre clinical series of HH patients.

Future directions

Assessment of longitudinal profiles would allow us to delineate trajectory over time and define the temporal relationship between neurodevelopmental comorbidities, such as autism, and evolution of seizures in more detail. It would also enable us to determine the influence of treatments, in particular surgery, on seizures, cognition and development.
Neurodevelopmental assessment of children with CPP-only presentations would allow us to determine whether this subgroup has a relatively benign course, as previously suggested [20].

Summary

Our findings have allowed us to conceptualize the atypical neurodevelopmental profiles in HH differently, as a developmental and epileptic encephalopathy. In addition, we have clearly demonstrated that structural characteristics of the hamartoma, in addition to the presence or absence of epilepsy, can be used to predict the clinical course, with implications for counselling, monitoring and treatment. ■

Key points

- Over half of children with HH had epilepsy; neurodevelopmental disorders were also highly prevalent.
- Epilepsy was associated with the presence of neurodevelopmental comorbidities.
- In many children with later onset seizures or no seizures, autistic behaviours and/or neurodevelopmental concerns arose first.
- Structural correlates for epilepsy and ID were identified.

Supplementary material.
Supplementary data and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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

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TEST YOURSELF

(1) Name a risk factor for neurodevelopmental comorbidity in children with HH.

(2) Which structural characteristics of HH are predictive of development of epilepsy and comorbidities?

(3) Autistic features often antedate the onset of seizures or occur in their absence. What could autism be attributed to, if not seizures?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.