RESEARCH ARTICLE

International Consensus on the Evaluation and Management of Hypothalamic Hamartomas

Results From a Modified Delphi Survey

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Abstract

Background and Objectives

Hypothalamic hamartomas (HH) are rare brain lesions associated with epilepsy and numerous comorbidities. Worldwide treatment is varied. There is a paucity of high-quality evidence to guide treatment. This study aimed to establish expert consensus on the evaluation and management of HH.

Methods

A modified Delphi survey was designed by the Medical Advisory Board of Hope for Hypothalamic Hamartomas and was conducted among 17 International League Against Epilepsy level II epilepsy surgery centers. The survey included 257 questions in round 1 and 81 refined questions in round 2, covering domains of diagnosis, imaging, medical and surgical treatment, neuropsychological and psychiatric evaluation, and care. Consensus was defined as ≥75% agreement using a 9-point Likert scale.

Results

Consensus was achieved on 82% of the questions. Key findings include the following: Diagnosis: Gelastic and dacrystic seizures are strongly associated with HH; 3T epilepsy protocol MRI is essential. Evaluation: Preoperative neuropsychological and endocrinologic assessments are important. Evaluation with further imaging (PET, SPECT, and magnetoencephalography) and intracranial EEG is not useful. Treatment: No consensus was achieved on first-line, second-line, or third-line antiseizure medications (ASMs). Surgical evaluation should begin at the start of the first ASM, with surgery recommended after failure of 2 ASMs. LITT is preferred for Delalande II and III HH. Postoperative care: MRI follow-up at 6–12 months recommended. Preoperative and postoperative cognitive, behavioral, psychosocial, and endocrinologic

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Supplementary Material

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Glossary

ASM = antiseizure medication; **DRE** = drug-resistant epilepsy; **FLAIR** = fluid-attenuated inversion recovery; **ILAE** = International League Against Epilepsy; **LITT** = laser interstitial thermal therapy; **MRgLITT** = MRI-guided LITT; **RFTC** = radio frequency thermocoagulation.

evaluations are emphasized. Domains: IQ, language, attention, executive function, academic achievement, adaptive function, and behavior (tantrums, rage, anxiety, and depression) are important.

Discussion

This Delphi process highlights an international consensus on aspects of HH management. Gelastic/dacrystic seizures are important at diagnosis. A 3T epilepsy protocol MRI is essential. Early epilepsy surgery evaluation is advised. Surgery should be pursued either by disconnective, ablative, or resective techniques. HH location, size, and surgical experience are essential for good outcomes. Postoperative MRI should be obtained 6–12 months and/or if ongoing seizures. Neuropsychological testing should be obtained at baseline, and 6–12 months postsurgically. Findings support a multidisciplinary, protocol-driven approach to optimize outcomes in patients with HH. Areas lacking consensus, such as specific endocrine testing and timing of certain interventions, warrant further research and standardization.

Introduction

Hypothalamic hamartomas (HH) are rare, congenital brain malformations that are usually associated with drug-resistant epilepsy (DRE) and a spectrum of neurodevelopmental, neuropsychological, and endocrine comorbidities.[1] HH syndrome affects approximately 1 in 200,000 individuals,[2] but management practices vary widely.[1,3] The characteristic gelastic seizure, or spells of mirthless laughter, often occurs without surface EEG correlate, which can complicate the work-up. These, and other typical dacrystic (or paroxysmal events of crying), seizures can be difficult for families or providers to recognize, adding to delayed care. The typical initial presentation involves a combination of DRE and/or endocrine dysfunction, such as precocious puberty and obesity.[4] Despite HH being linked to precocious puberty in 1934, to seizures in 1958,[5] and the epilepsy syndrome being well-characterized in 1988,[6] there is still a paucity of high-quality data and no consensus guidelines many decades later to guide diagnosis and treatment. Given there are underrecognition of the disease, the deep location of the epileptogenic lesion in the hypothalamus, the complicated presentation and management of the HH syndrome, the broad and distinct comorbidities (some psychiatric, several endocrine) which are underappreciated or known, and the variety of surgical management strategies, broader guidance is needed beyond existing management strategies for typical cortical drug-resistant epilepsies. The purpose of this study was to establish consensus on evaluation and management strategies for HH using a modified Delphi process from experts across international epilepsy centers.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved as exempt by the Institutional Review Board of Children's National Hospital in Washington, DC.

Survey Design and Representativeness

A modified Delphi survey regarding the diagnosis and management of HH was designed to evaluate core areas as proposed at the 2019 International Symposium on Hypothalamic Hamartomas in Washington, DC. The first round of the survey was discussed at the 2022 International Symposium on HH in Calgary. The second round of the survey was sent after the Calgary meeting, with final results presented at the 2025 International Symposium on HH in Barcelona. These Symposia are run by Hope for Hypothalamic Hamartomas, the largest international patient-driven and family-driven nonprofit organization dedicated to research and treatment for HH. The questions for the survey were designed by the Medical Advisory Board of Hope for HH, which includes world experts in HH medical, surgical, and comorbidity management comprised of pediatric epilepsy surgeons, pediatric epileptologists, neuropsychologists, endocrinologists, and researchers with extensive experience in basic, clinical, and translational research on the disease. To ensure inclusiveness, survey question topics were generated by focus groups on core areas at the International Symposium which included clinicians, researchers, patients, and caregivers from around the world. The limited existing evidence, where available, was reviewed or discussed by the session leaders. These core areas included clinical, surgical, endocrine, imaging, and neuropsychology/psychiatry. The initial phase included drafting and review of questions. Survey questions were written to address issues related to primary diagnosis, treatment, and care decisions (diagnostic testing and medical treatment); surgical treatments (selection/choice of surgical approaches and evaluation of complications); neuroimaging (prediagnosis, as related to the surgical evaluation, and postoperative imaging recommendations); and recommendations for evaluation and management of neuropsychological and psychiatric comorbidities.

A modified Delphi survey was conducted among 24 invited International League Against Epilepsy (ILAE) level II epilepsy centers based on participation in ILAE Pediatric Epilepsy Surgery Task Force surveys that established technical aspects and worldwide criteria for pediatric epilepsy surgery centers.[7,8] These include ILAE Pediatric Epilepsy Surgery Task Force members and ILAE-certified centers from low-middle to high-income countries. Centers also had to be recognized by the Hope for HH Medical Advisory Board as having experience in treating HH.

The survey was conducted in 2 rounds. The first round consisted of 257 questions taking about 1 hour to complete.

Each center had a designated survey respondent. Domain-specific answers were provided by subspecialist experts at each center through the designee. For round 1, a 9-point Likert scale was clustered for analysis as 1–3 indicating "important/necessary," 4–6 indicating "no strong view," and 7–9 indicating "not important/unnecessary." Answers achieving "important/necessary" or "not important/unnecessary" categories with ≥75% of responding centers achieved consensus. Questions with 55%–74% agreement were revised and re-evaluated in round 2. Here, questions were clarified or reworded if poorly phrased. Questions with near consensus (65%–74% agreement from round 1) were presented with the near-consensus result. Round 2 consisted of 81 questions. Questions in round 2 were voted on using up or down scoring (e.g., agree or disagree with the majority). Comments were collected (if needed) for those in disagreement. Consensus was defined as ≥75% agreement of responding centers. Questions for round 1 and round 2 are listed in eAppendix 1 and 2, respectively.

Data Availability

Survey data are available on reasonable request from a qualified investigator.

Results

Table 1 summarizes survey respondent and surgical center characteristics.

For round 1, identified respondents included 32 specialists from 17 centers (70% of centers) in 5 continents: North America (n = 8), Europe (n = 6), Asia (n = 1), Australia (n = 1), and South America (n = 1). Of the 257 questions in round 1, consensus could not be reached for 45 (18%) questions. For round 2, of 81 questions administered, there were 3 clarifying questions proposed, and consensus could not be achieved in 2 (2%) questions.

Responses to the survey were as follows (organized by core section, with clustered Likert scale responses for each answer provided).

Primary Diagnosis

The diagnosis of HH should be considered when presenting seizures are gelastic (likely), dacrystic (likely), intractable (no consensus), and focal (unlikely); when endocrine symptoms are present (likely).

Treatment and Care: Evaluation

Diagnostic Testing

Table 2 summarizes the key recommendations regarding diagnostic testing for HH. The only unanimous response was that a 3T MRI brain with an epilepsy protocol including high-resolution 3D T1-weighted sequence with ≤1 mm^3 voxels, 3D fluid-attenuated inversion recovery (FLAIR), and T2 sequences in 2 planes is important (essential per ILAE guidelines).[9,10] Additional MRI sequences were not viewed as important.

Endocrine and neuropsychological testing was felt to be important at the diagnosis of HH, as well as part of the presurgical evaluation, which for practical purposes might be initiated at diagnosis (see below).

Gelastic Epilepsy

When focusing on gelastic epilepsy, participants reached consensus that gelastic seizures are likely present longer than reported when the parent is questioned about their presence in history-taking. There was agreement as well that parents are often unaware of the presence of gelastic seizures, which can be diagnosed on video EEG. Gelastic seizures are not pathognomonic of HH and may arise from temporal or frontal lobe generators, which may sometimes be clarified by video EEG. Antiseizure medication (ASM) choice should be based on the specific seizure type being treated.

Respondents agreed that patients are diagnosed when they exhibit gelastic seizures. Most patients have a longer history of gelastic seizures before their diagnosis when questioned directly. MRIs should be re-reviewed, and new, repeat 3T epilepsy protocol brain MRI should be considered if not performed in patients with clear gelastic seizures and reportedly negative MRI. In some cases, parents and patients are not aware of gelastic seizures but that they can become evident from video EEG monitoring. As in Table 2, respondents were also asked about the importance of cell phone video which did not achieve consensus.

Treatment and Care: Medical Treatment and Beginning Surgical Evaluation

There was no consensus about first-choice ASM, but oxcarbazepine/carbamazepine and levetiracetam/brivaracetam were voted as top choices. There was no consensus on second-choice or third-choice ASMs. Table 3 summarizes the results of recommendations for first-choice, second-choice, and third-choice ASMs in HH-related epilepsy. There was agreement that epilepsy surgery should be considered after the failure of the

Table 1 Center and Respondent Characteristics

	n (%) or mean (range)
Specialist type	
Neurologists	4 (12.5)
Pediatric neurologists	8 (25)
Neurosurgeons	12 (37.5)
Neuropsychologists	4 (12.5)
Endocrinologist	1 (3.1)
Neuroradiologists	3 (9.4)
Other	1 (3.1)
Average number of cases per year	10.5 (2–25)
Average number of total cases	67 (10–250)
Centers	
NHO Nishiniigata Chuo Hospital, Niigata, Japan	
The Royal Children's Hospital, Melbourne, Australia	
University Medical Center, University of Freiburg, Germany	
Bambino Gesù Children's Hospital, Rome, Italy	
Foundation Hospital, Paris, France	
Hospices Civils de Lyon, Lyon, France	
Aix Marseille University, Marseille, France	
Great Ormond Street Hospital, United Kingdom	
São Paulo Epilepsy Clinic, São Paulo, Brazil	
Alberta Children's Hospital, Calgary, Canada	
Hospital for Sick Children Toronto, Canada	
Boston Children's Hospital, MA	
Phoenix Children's Hospital, AZ	
Children's National Hospital, Washington, DC	
Children's Hospital of Philadelphia, PA	
Texas Children's Hospital, Houston, TX	
Nicklaus Children's Hospital, Miami, FL	

This table presents the expertise of survey respondents. Other means the training section was left blank. The mean (and range) number of annual and all-time surgical hypothalamic hamartoma cases performed by centers.

second appropriately selected, adequately dosed ASM. However, there was agreement that the presurgical evaluation should begin coinciding with the start of the first ASM. There was no consensus about surgical consideration after the failure of the first ASM. There was consensus not to offer surgery without trial of an ASM, and waiting beyond failure of 3 or more ASMs is too late.

Surgical Treatment

There was agreement that the surgical strategy should disconnect or completely remove the HH, or to disconnect and partially remove the HH leaving some tissue behind. There was also no consensus about pursuit of repeat surgery to achieve seizure freedom. On clarification, there was agreement that for patients with seizures, an intervention with the goal to remove or disconnect the HH is most promising, and there was agreement that a disconnection may lead to seizure-free outcome even if the majority of the HH tissue remains untouched.

Surgical Treatment Availability

Eighty-eight percent (n = 15/17) of centers offer endoscopic or transcallosal resection; 82% (14/17) offer skull base surgery.

Table 2 Consensus Recommendations on Diagnostic Testing

Diagnostic testing		Caveat/explanation
Important (I)		
	Video EEG	Can be falsely assuring or localizing
	3T epilepsy protocol brain MRI*	1.5T MRI (I) but 3T is preferred
	Endocrine testing	Both endocrine + neuropsychological
	Neuropsychological testing	testing (I) at diagnosis
Near consensus		
	Cell phone video	Near consensus, but 73% (I)
Not important (NI)		
	Routine EEG	
	3D source localization	
	Magnetoencephalography	
	Intracranial EEG	
Neuroimaging		
Important (I)		
	3T HARNESS protocol:	
	High-res 3D T1-weighted (≤1 mm^3 voxels)	
	3D FLAIR	
	T2-weighted sequences in 2 planes	
No consensus		
	Diffusion weighted imaging	
Not important (NI)		
	CT	
	Ultrasound	
	fMRI	
	FDG-PET	
	MR spectroscopy	
	Ictal SPECT	

Abbreviations: FDG = fluorodeoxyglucose; FLAIR = fluid-attenuated inversion recovery; HARNESS = Harmonized Neuroimaging of Epilepsy Structural Sequences.
This table summarizes the Delphi consensus results on diagnostic testing. The left column summarizes the panel vote. The middle column summarizes the tests. The right column describes caveat statements that achieved consensus from the panel or has explanatory information.

Seventy-one percent of centers (12/17) offer laser interstitial thermal therapy (LITT), gamma knife surgery, or radiofrequency thermocoagulation. A minority of centers, 20% (3/15), offer high-frequency focused ultrasound (HiFUS). Endoscopic, transcallosal, skull base surgeries, and HiFUS do not require referrals, whereas LITT, gamma knife surgery, and radio frequency thermocoagulation (RFTC) do.

Surgical Treatment: Considerations

There was consensus on the importance of surgical experience with the specific procedure being offered. The size and location of the lesion are important for selection of surgical strategy. The severity of the epilepsy was rated as important. The center should have expertise in management of HH (important). There was no consensus about the age at which surgery should be offered. There was consensus agreement that insurance status is not important when considering surgery for a patient with HH.

Although there are several classifications of HH, the Delalande classification is most widely adopted. Briefly, the Delalande schema is as follows: class 1 (horizontal insertion

Table 3 Voting for First, Second, and Third-Choice ASMs

ASM	First	Second	Third
Oxcarbazepine/carbamazepine	7	4	
Levetiracetam/brivaracetam	5	4	3
Valproic acid	2	1	2
Phenytoin	1	1	1
Clobazam	1	2	1
Lamotrigine		4	3
Lacosamide		1	1
Topiramate		1	2
Vigabatrin			1
Zonisamide			4

Abbreviation: ASM = antiseizure medication.

below floor of third ventricle), class 2 (vertical insertion along the wall of third ventricle), class 3 (horizontal and vertical attachment above and below the floor of third ventricle), and class 4 (giant HH greater than or equal to 8 cm^3).[11] Table 4 summarizes the survey results for minimum age and specific treatment recommendations by Delalande class.

After Diagnosis

There was consensus agreement that there should be referral for endocrine evaluation for all patients with HH. Ideally, the endocrine follow-up can be timed to coincide with neurology follow-up (care coordination). Respondents disagreed with the statement that follow-up is not needed.

MRI

MRI is essential prediagnosis (consensus). Once confirmed on high-resolution epilepsy protocol MRI, there was agreement that additional preoperative MRI sequences are unnecessary. Seventy percent of respondents (12/17) obtained an intraoperative MRI (this question did not specify for which type of procedure). There was no consensus for obtaining a postoperative MRI on the same day, within 24 hours of surgery, or within 48 hours of surgery. MRI within 1–2 weeks postoperatively was rated as too late. There was consensus that a single postoperative MRI should be obtained within 6–12 months of surgery, but no consensus about the exact timing. Once obtained, further postoperative MRI is only recommended if there are ongoing seizures (consensus).

Behavioral/Cognitive Focus

Neuropsychological evaluation for cognition was rated important. Behavioral and psychosocial evaluations were also ranked important. Psychiatric evaluation was recommended for treatment need and medication prescription. There was no consensus on the need for occupational therapy or for physical therapy.

Evaluation

The behavioral/cognitive evaluation was ranked as important for the following reasons: (1) to establish baseline functioning; (2) to determine the presence of comorbidity such as intellectual and developmental disability, autism spectrum disorder, or attention-deficit/hyperactivity disorder; (3) to determine necessary interventions (behavioral, medication); (4) to determine necessity of support services for school; and (5) to determine necessity of support services for the family.

Within the cognitive evaluation, respondents felt the following areas were important for testing: (1) attention/executive function, (2) memory, (3) language, (4) IQ, and (5) academic achievement. There was no consensus on the importance of evaluation of visuospatial and motor skills.

For the behavioral evaluation, respondents ranked the following areas as important for assessment: (1) anxiety, (2) mood/depression, (3) behavior, and (4) rage/aggression.

Respondents also rated assessment of social functioning as important in the following areas: (1) social skills/peer relationships, (2) family functioning/parental stress, and (3) atypical behaviors (including mirthless laughter and atypical eating). There was no consensus if the presence or absence of seizures alters these recommendations.

Table 4 Consensus on Age Consideration and Treatment Options by Delalande Class

	LITT	GKS	RFTC	Endo	Trans CC	Skull base	Med Rx/no surg
Minimum age	NC	NC	NC	No limit[a]	No limit[a]	No limit[a]	
Delalande 1	NC	NC	NC	NC	NC	NC	Inappropriate[a]
Delalande 2	Appropriate[a]	NC	NC	NC	NC	Inappropriate[a]	Inappropriate[a]
Delalande 3	Appropriate[a]	NC	NC	NC	NC	NC	Inappropriate[a]
Delalande 4	NC	NC	NC	NC	NC	NC	Inappropriate[a]

Abbreviations: Endo = endoscopic resection; GKS = gamma knife surgery; LITT = laser interstitial thermal therapy; NC = no consensus; RFTC = radio frequency thermocoagulation; Trans CC = transcallosal.
[a] Indicates consensus.

Preoperative Evaluation

Respondents rated numerous domains of cognition and behavior as important for preoperative evaluation (which may be the same as initial evaluation). These included (1) IQ, (2) language, (3) visuospatial skill, (4) attention, (5) executive function, (6) memory, (7) motor skills, (8) academic achievement, (9) adaptive function, and (10) social cognition. In addition, preoperative evaluation for anxiety, depression, behavioral tantrums, rage and aggression, as well as atypical behaviors were rated as important.

Postoperative Evaluation

The timing and necessity of postoperative neuropsychological and psychosocial evaluations were rated. Respondents felt these evaluations should occur at minimum once (important), and preferably with ongoing surveillance (multiple evaluations) (important). There was agreement that postoperative evaluation should occur between 6 and 12 months without consensus being achieved for 6 or 12 months; 73% of respondents (plurality) recommended 12 months postoperatively for evaluation. One month postoperatively was rated too early, and 18 months or longer was too long. There was no consensus about whether specific age considerations should alter these recommendations.

Discussion

HHs are rare, developmental brain malformations that cause a syndrome of drug-resistant epileptic encephalopathy. There are numerous comorbidities associated with the disease and its treatment. Despite knowledge of the existence of HH and its association with precocious puberty (>90 years), with seizures (>60 years), and with the epilepsy syndrome (>35 years), there is still wide variability in the diagnosis and treatment of the disorder. This international, multidisciplinary, modified Delphi survey of practitioners from 17 ILAE level II epilepsy centers in 8 countries across 5 continents establishes consensus recommendations for the diagnosis, management, and treatment of the HH syndrome and its wide-ranging comorbidities.

Overall, this international, modified Delphi survey achieved consensus on 82% of questions, helping to clarify areas of importance the diagnosis and medical/surgical management of the HH syndrome and its comorbidities.

The Discussion is organized into 2 sections, the first focusing on issues related to the diagnosis, the second on treatment of HH, with subsections of thematic review and highlighted consensus recommendations.

Neuroimaging was reviewed first. There are no current guidelines for the diagnosis and treatment of HHs. MRI has been recommended as the gold standard for imaging (since the 1980s) due to its superior resolution and ability to clearly delineate anatomical associations.[1,3,6] The lesions are easily distinguished from normal hypothalamic grey matter and best appreciated on T2-weighted sequences.[12] The 2019 ILAE Consensus on Structural Neuroimaging for Patients with Epilepsy recommends the Harmonized Neuroimaging of Epilepsy Structural Sequences high-resolution 3T (or 1.5T when 3T unavailable) MRI for all patients with new-onset seizure.[9] The HARNESS protocol includes high-resolution 3D T1-weighted sequence, 3D FLAIR, and 2D coronal T2-weighted sequence acquired perpendicular to the long axis of the hippocampus. Pediatric imaging guidelines include T2 imaging in 2 directions.[10] Thus, T2 sequences should be obtained in any pediatric patient with suspicion for HH. High-resolution epilepsy protocol MRI will detect HH, but the neuroradiologist/epilepsy team needs to be skilled and specifically looking for HH. New clinical data that raise concern for HH syndrome should prompt re-review of prior neuroimaging and neurophysiologic work-up to try to identify a lesion.

Consensus was achieved for neuroimaging in the following areas. Gelastic and dacrystic seizures (characterized as mimetic automatisms in the 2025 ILAE classification of seizures[13]) are considered important when considering the primary diagnosis. High-resolution epilepsy protocol 3T MRI is essential to the initial evaluation. Head CT, ultrasound, functional MRI, FDG-PET, MR spectroscopy, and ictal SPECT were rated as not important and are unnecessary.

Next, EEG was considered. The role of EEG holds important limitations and requires skill in interpretation. Although gelastic seizures are common at onset (up to 77% of patients), 75% of gelastic seizures have no associated scalp EEG correlate; seizures with ictal EEG correlate have high rates of false localization suggesting scalp EEG may be of limited use in seizure localization.[14,15] EEG findings, in particular, should not influence the surgical decision given their unreliability. The video clinical characterization of events, however, may be diagnostic with the EEG best not being overinterpreted. The HH tissue is known to be the generator of gelastic seizures as confirmed by stereoEEG.[16] There is no role for stereoEEG in the diagnosis and management of HH syndrome.

Consensus was achieved for EEG as follows. Routine EEG was rated as not important. Video EEG was rated as important (with disclaimer of potential for false negativity or false localization/lateralization). Intracranial EEG was rated as not useful in the initial diagnosis of HH. Additional neurophysiologic studies such as 3D source localization and magnetoencephalography were also ranked not important.

Psychiatric, behavioral and cognitive comorbidities were reviewed. HH syndrome is associated with a wide array of neuropsychological, cognitive, behavioral, and psychiatric comorbidities. Fifty-five percent of patients with HH are affected by a psychiatric comorbidity.[17] There are high rates of oppositional defiant disorder, attention-deficit/hyperactivity disorder, conduct disorder, autism spectrum disorder, and other

affective disorders.[18-21] These comorbidities have similar rates of presentation as seen in other focal lesional epilepsies. The exception is the rage attacks which are commonly seen in HH. Behavioral comorbidities may predate seizures.[1]

Aggression is more likely with the following: male sex, younger age at seizure onset, presence of intellectual disability, or multiple seizure types.[22]

Presurgical developmental delay or intellectual disability is reported in ~50% of patients with some centers now using these data to inform surgical timing.[17,23] Patients with HH often have visual and verbal memory deficits, executive dysfunction, and other wide-ranging cognitive dysfunction.[24] Deficits in long-term retrieval and processing speed are frequent.[25] Similar to epilepsy in general, worse cognitive functioning is associated with early age at seizure onset, more frequent seizures, larger lesion size, and taking more ASMs.[26-28] Studies from more recent surgical cohorts with minimally invasive techniques show cessation of cognitive declines and sometimes improvement postoperatively.[27-29]

Consensus for psychiatric, behavioral, and cognitive comorbidities was achieved as follows. There were consensus recommendations on preoperative evaluation. Neuropsychological evaluation was rated as important especially for assessing cognitive, behavioral, and social impacts on the patient. Behavioral and cognitive evaluations should be established at baseline including comorbidity assessments and should be rechecked 6–12 months postoperatively. The emphasis of these evaluations should include focusing on tantrums, rage, memory, IQ, language, attention, executive function, academic achievement, and adaptive skills. Given the high rate of psychiatric comorbidities experienced by patients with HH, it is recommended to obtain psychiatric evaluation at baseline to evaluate for medication management and therapeutic needs.

Endocrine evaluation was considered. There are several endocrinologic problems associated with HH syndrome. Between 40% and 67% of patients present with precocious puberty,[30,31] which may require ongoing treatment even after surgical treatment. Other endocrine disorders include advanced skeletal maturation (from the central precocious puberty) but with reduction in growth velocity, secondary (thyroid-stimulating hormone) or tertiary (thyrotropin-releasing hormone) hypothyroidism, and hypothalamic obesity syndrome.[4] Postoperatively, hypernatremia (from arginine vasopressin deficiency [diabetes insipidus]) can occur; growth hormone deficiency, adrenal insufficiency, hypogonadism, hypothyroidism, and weight gain are also reported.[32]

Regarding endocrine evaluation, consensus was achieved as follows. Endocrine referral should be pursued for all patients with HH at diagnosis. There was no consensus on which endocrine tests to be performed at diagnosis, or across treatment. It was recommended to have multidisciplinary endocrine follow-up (especially postoperatively) to be timed with neurologic follow-up when possible.

The second half of the Discussion focuses on issues related to treatment of HH.

Medical management of HH was considered first. Most patients with HH syndrome develop DRE that usually starts with gelastic seizures.[1,33] The purpose of ASM treatment is to try to control seizures and prevent progression of epilepsy, and especially to limit generalized tonic-clonic (convulsive) seizures due to their risk of morbidity and mortality. Treatment strategies should be individualized to the patient.[4]

Consensus recommendations regarding medical managemente of HH were as follows. There was no consensus achieved on optimal first-choice ASM. However, sodium channel drugs such as oxcarbazepine/carbamazepine, and Synaptic Vesicle Glycoprotein 2A (SV2A)-receptor modulators such as levetiracetam/brivaracetam received the most votes as first options. There are no data for superior efficacy of any of the ASMs. Of note, all ASMs are used with the goal of seizure control, and all have different side effect profiles. These known risks must be weighed against efficacy when used. Consensus failed to be achieved for second-line or third-line ASMs.

Surgical management strategies for HH were discussed next. There are numerous surgical strategies that can be used to treat HH syndrome. These include open vs minimally invasive techniques, as well as various ablative procedures.

High-level recommendations from Jacobs and Hildebrand[3] were synthesized from recent meta-analyses of more than 500 patients[34-36]: (1) minimally invasive procedures are more effective and less complicated than open (micro)surgical techniques; (2) radiosurgical techniques have lower complication rates but delays in seizure cessation; and (3) overall seizure-free rates are higher than ongoing medical therapy, and early surgical intervention should be offered.

A systematic review/meta-analysis of 64 studies and 517 patients evaluated surgical outcomes and risks across all modern HH surgical options.[36] The major findings were that radio-frequency thermocoagulation and MRI-guided LITT (MRgLITT) achieved the highest rates of seizure-free outcome (78.5% and 74.5%). Surgical failure is more likely if there are multiple seizure types or if the patient had prior surgery.

This meta-analysis also directly compared postoperative complications across different techniques at both study level and individual patient data level. From the study-level analysis, Stereotactic radiosurgery (SRS) was the safest option with a pooled major complication rate of 0.0% (95% CI 0.0%–1.4%). Open microsurgery had the largest rate of major complications with pooled proportion of 29.1% (9.5%–

54.2%). There were no differences in major complications between RFTC and MRgLITT.

From the individual participant data meta-analysis, overall postsurgical complications were reported most in open microsurgery (54.6%) and least in SRS (1.8%). *Major complications* were also most common in open microsurgery (33%) and least in SRS (1.8%). *Neurologic complications* (motor/visual deficits) were reported in 2.8% overall. They were most common in MRgLITT (6.2%) and open microsurgery (5.2%); and least common in endoscopic, SRS, or RFTC (0.0%). *Surgical complications* (hemorrhage or infection) were reported in 0.3% overall. They were most frequent in open microsurgery (1.0%): and least common in endoscopic, SRS, MRgLITT, or RFTC (0.0%). *Hypothalamic complications* (hyperphagia, poikilothermia, and polydipsia) were reported overall in 7.0%. They were most frequent in open microsurgery (16.5% and endoscopic (6.7%), infrequent in SRS (1.8%); and least common in MRgLITT and RFTC (0.0%). *Endocrine complications* (hormone deficiencies and diabetes insipidus) were reported in 4.9% overall. They were most common in open microsurgery (13.4%), infrequent in RFTC (3.2%), endoscopic (2.2%); and least common in SRS or MRgLITT (0.0%). *Behavioral complications* (behavioral disturbances) were reported in 0.9% overall. They occurred most in open microsurgery (2.1%); and least frequently in endoscopic, SRS, MRgLITT, or RFTC (0.0%). *Cognitive complications* (any deficit in cognitive domain especially memory) were reported in 3.4% overall. They were most commonly reported in MRgLITT, (9.2%), open microsurgery (4.1%), endoscopic (2.2%); and least common in SRS or RFTC (0.0%). Of note, complication rates (including many 0% rates) are as reported from this study design, which may not represent full real-world experience, and may suffer from underreporting. Future prospective and randomized controlled trial data would more clearly delineate complication rates.

Consensus recommendations regarding surgical management of HH were as follows. The panel felt it was important to begin the consideration of epilepsy surgical evaluation at the time of diagnosis after starting the first ASM and certainly when the second ASM has failed the child. This is in line with ILAE Surgical Therapies Commission Recommendations meant to prevent surgical delays, especially in highly epileptogenic lesions in noneloquent regions.[37] There were questions to operate at diagnosis or after the failure of 1 ASM; some respondents felt this was enough of a threshold to perform surgery; however, this did not achieve consensus. Emerging data from other highly epileptogenic lesions, such as focal cortical dysplasia, suggest consideration of surgery after the failure of just 1 ASM given the high rate of conversion to DRE and noted good surgical outcomes in this pathology.[38] Early epilepsy surgical evaluation (before failure of 2 ASMs) is associated with better surgical outcomes,[39] and early epilepsy surgical intervention may lead to fewer comorbidities.[40] Surgery should be pursued with the goal of disconnection or removal of the epileptogenic HH tissue. Overall, epilepsy surgery for HH is safe with limited morbidity and no significant risk of mortality. After surgery, a repeat 3T epilepsy protocol MRI should be obtained between 6 and 12 months postoperatively, with further imaging as needed if ongoing seizures after this time. The recently reported data on surgical complications noted above replace clinical views on surgical approach risks that were qualitative, and the term "common" was not defined.

There are several potential limitations to this modified Delphi survey. There is potential selection bias due to the nature of the study design being based on prior participation in a pediatric neurosurgical survey among ILAE level II epilepsy centers. The survey responses are skewed to North American and European centers, and some treatment options available in certain regions may not be yet available broadly. There was limited representation of Asian and South American centers (although several invited to participate), and no African centers. For surgical recommendations, some centers may have been biased toward their center's expertise in certain (few) techniques. These recommendations represent the best available (although potentially biased) expert opinions of ILAE level 2 epilepsy surgical centers whose broad clinical exposure with HH management affords expertise in surgical recommendations, even for procedures not performed at those institutions. Future prospective trials could help to clarify surgical efficacy and risks more rigorously, but are difficult to implement given the rarity of the disorder. As much as possible, this survey was designed to provide optimal care through diagnostic and treatment recommendations that could be implemented in most care settings. Furthermore, although this modified Delphi survey had broad participation with at least 32 multidisciplinary specialists from 17 international epilepsy centers, there is potential nonresponse bias. A limitation is that not all centers acknowledged subspecialist training backgrounds. Thus, these survey results likely represent a broader perspective than the 32 identified participants. Some consensus statements provide general recommendations without the clarity of specification such as which specific endocrinologic testing should be obtained. Rage attacks remain commonly reported but poorly described; their characterization and ontogeny warrant further systematic study.

HH syndrome is a rare disease that is often associated with intractable epileptic encephalopathy and numerous endocrine, cognitive, behavioral, neuropsychological, psychiatric, and psychosocial comorbidities. Given the rarity of the disorder, there has been variable treatment of patients with HH across the world. Here, a multidisciplinary group of experts convened from 17 international ILAE level II epilepsy centers to create modified Delphi consensus recommendations on all aspects of the diagnosis and treatment of the HH syndrome: from initial identification of the lesion, medical and surgical recommendations, and the identification and treatment of numerous associated comorbidities. Early consideration of

epilepsy surgery should be pursued. These suggestions aggregate broad, intercontinental experience with this rare disease and form the basis for standardizing and improving care for patients affected by HH worldwide. This consensus helps to identify gaps in current evidence. There are various presentations of the HH syndrome and its comorbidities and future multicenter and prospective controlled studies need to be designed to identify and fully address best practices in management, and in particular to identify the best surgical options for patients.

Author Contributions

N.T. Cohen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. X. Li: major role in the acquisition of data; analysis or interpretation of data. M.M. Berl: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. C.O. Oluigbo: major role in the acquisition of data; analysis or interpretation of data. H. Shirozu: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S.F. Berkovic: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Zacharin: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. W. Maixner: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Schulze-Bonhage: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K. Klotz: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. N. Specchio: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Ferrand-Sorbets: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Bulteau: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A.A. Arzimanoglou: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Regis: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J.H. Cross: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M.M. Tisdall: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. H. Richardson: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Cukiert: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Cukiert: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Jacobs: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E.J. Donner: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P.L. Pearl: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J.F. Kerrigan: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A.A. Wilfong: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K.C.J. Yuen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D.J. Dlugos: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Curry: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. I. Ali: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Ragheb: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Soeby: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E. Webster: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. W.D. Gaillard: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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