Hypothalamic Hamartoma Syndrome

Also known as: HH

Overview

Hypothalamic hamartomas (HH) are lesions that arise in the ventral hypothalamic region. The syndrome is commonly associated with a spectrum of clinical, endocrinologic, and psychosocial comorbidities including refractory epilepsy, precocious puberty, and rage behaviours. Additionally, HH syndrome may include the evolution of an epileptic encephalopathy with developmental regression, psychiatric and behavioral comorbidities. Neuropsychological, sleep and endocrine disorders are also common. For most, the initial seizures are gelastic seizures and begin early in life, often at less than 1 year of age, and are difficult to recognize. Gelastic seizures are the most specific symptom associated with HH and appear as laughter (often mirthless) or giggles that an individual cannot control and happen without any obvious trigger. In the very young, they are often mistaken for colic or reflux. They usually occur daily, and for some there may be hundreds per day. The epilepsy symptoms progressively change, with the appearance of other seizure types such as atypical absences, focal and generalized tonic-clonic seizures and drop-attacks. It is often not until these other seizure types manifest that an HH is discovered. For many individuals, the process of getting a correct diagnosis can take months or years. Achieving early accurate diagnosis is critical and surgical intervention is often recommended earlier in the treatment plan rather than a "wait and see" approach.

Incidence and prevalence

The prevalence of epilepsy in HH is estimated to be 1 in 200,000 children with a slightly higher number of males versus females. This estimate, which may be low since HH is hard to detect, suggests that there are about 30,000 in the world living with HH. Approximately 5% of all HH cases are associated with Pallister-Hall syndrome. There are likely to be people with epilepsy in whom the syndrome remains undiagnosed or misdiagnosed.

Aetiology

Aetiology is not yet fully understood, but it is suspected that genetic factors contribute. One large study has reported a sonic hedgehog gene abnormality (e.g. GLI3, PRKACA) in about one-third (~ 37%) of sporadic, non-syndromic cases. In most syndromic cases (with Pallister-Hall Syndrome), where molecular testing is performed, a genetic abnormality in the GLI3 gene is found to be the cause. There is emerging evidence that cilia gene (e.g. DYNC2H1) abnormalities can also cause HH in a significant minority of cases and research into cilia genes is on-going. This may mean that HH is ultimately reconceptualized as a ciliopathy. Genetic counselling is recommended for all Pallister-Hall cases, where the GLI3 abnormality can be transmitted from a parent to their child. It is not currently recommended for non-syndromic cases, however that may change depending on further research into the cilia gene abnormalities as at least some of these can be transmitted. In both groups (non-syndromic or syndromic) of children with HH, determining the underlying genetic cause may have implications for future therapeutic approaches.

Diagnosis of HH

Diagnostic evaluation of HH remains challenging. Due to the depth of the lesion, scalp EEG may be normal without evidence of interictal abnormality; even a regular surface EEG during a seizure can be difficult to localize or may be misleading because by the time the seizure activity leaves the HH and makes its way to the brain surface, the EEG cannot "see" where it came from initially. The hamartoma can also be difficult to identify on imaging due to its small size and location, even by experienced neuroradiologists, who may be more accustomed to searching for anatomical lesions in the cortex, the more typical location of seizure onset, rather than subcortical regions. A high-resolution 3Tesla brain MRI with epilepsy specific protocol including thin cut 3D T1 (¡ 1mm3 voxel) weighted sequences, T2 weighted and FLAIR sequences (minimum two planes, 3D better) is recommended to identify an HH. MRI technicians often use the following protocol sequence parameters:

- 3D T1W SPGR, axial 0.9mm isotropic voxels
- Sag T1W – min TE; 3mm slice, 0.5mm gap; FOV 20cm
- Sag T2W(FSE) – 2mm slice no gap; FOV 20cm
- Cor T2W(FSE) – 2mm slice no gap; FOV 16cm
- Cor T1W – 3D SPGR; 2mm slice; FOV 24cm – recon for axial
- Axial T2W(FSE) – routine brain

The interpretation of this imaging often requires specific expertise, usually more readily available at skilled paediatric epilepsy centres.

Age of seizure onset

Age of onset is typically less than a year for gelastic seizures, and between two to seven years of age for additional focal seizure types, both of which are often refractory to medical treatment.

Seizure types at presentation

Gelastic seizures are almost always the first seizure manifestation of HH. Most individuals do not feel happy and in fact, may feel anxiety and panic when they are forced to laugh at inappropriate times. Other common features of a gelastic seizure are:

- The person may look startled or even have a look of panic or fear.
- There can also be an unpleasant feeling in the stomach (like butterflies), a tickling in the chest or headache. Lip smacking or frequent swallowing may be seen.
- The eyes may seem vacant and move up and to one side.
- There often is a slight smile that seems a bit forced and laughter or grunting that seems unusual or not appropriate at that time.
- May be triggered by loud noises or sudden actions.
- Often occur as the individual is falling off to sleep.

These seizures can occur many times a day. In some cases, over 100 a day. The seizure may present asymmetrically, with the stronger grimacing appearing on the side of the face contralateral to the HH attachment within the third ventricle. Sometimes crying (dacrystic) seizures may be seen.

How seizure types change over time

Seizures often evolve to include focal seizures with impaired awareness and these may resemble those observed in temporal lobe epilepsy. Generalized seizures may also occur including atypical absences, tonic, atonic and generalized tonic-clonic seizures. Epileptic spasms are occasionally seen.

Treatment

Anti-seizure medications (ASM), although necessary to reduce the risks of prolonged seizures, are usually not efficacious and overtreatment should be avoided. Currently, there are several surgical options for HH; disconnection or ablation is the surgical aim. Which surgical approach to use is based upon location, size, and attachment of the hamartoma. Approaches include Gamma Knife radiosurgery, stereotactic radiofrequency thermocoagulation, MRI-guided laser therapy, endoscopic resection and transcallosal resection. MRI-guided focused ultrasound thermoablation is currently in clinical trials for HH. Appropriate surgical intervention can achieve total or partial seizure control but may not reverse encephalopathy.

Comorbidities

HH is associated with a varying comorbidity profile that includes neurodevelopmental, behavioural, endocrine and psychiatric dysfunction. Precocious puberty presents in around a third of cases – and is often the clue that effects diagnosis. Psychiatric comorbidities exist in over 50% of children. Rage attacks, as well as less severe aggressive behaviours and attentional problems, are common. Cognitive impairments are also common, and these appear to be progressive in half of cases. In view of the apparent relationship between the epilepsy onset and neurocognitive difficulty, the syndrome is considered an epileptic encephalopathy, with increased seizure burden contributing to worse cognitive outcomes.

Review the impact of seizures, drugs & comorbidities on:

Overall well-being and day-to-day activities

Mental health

Physical health

Independence

Behaviour

Provide patient and/or carer with:

Access to multi-disciplinary team including neurology, endocrinology, neuropsychology and neurosurgery with experience in diagnosing and treating rare forms of epilepsy

Genetic counselling

Counselling re SUDEP and risk management

Patient, carer & employer support requirements (neuropsychological evaluation, guidance, potential psychiatric support)

Hypothalamic Hope Hamartomas

Giving Hope. Getting Answers.

Patient groups:

Hope for Hypothalamic Hamartomas

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Overview

A hypothalamic hamartoma (HH) is a rare tumour or lesion of the hypothalamus, present from birth. Hypothalamic hamartoma syndrome can be hard to diagnose and even more difficult to treat. HH can cause many types of seizures and other symptoms. The hallmark seizure type is gelastic seizures – episodes of uncontrolled, often mirthless, laughter. In infancy gelastic seizures can be mistaken for reflux or colic. Because HH is rare, it is not a common cause of developmental delay; however, infants and young children with HH may miss critical developmental milestones in speech, crawling, walking, and cognition. Diagnosing the initial seizures can be hard since symptoms are usually missed or not considered seizures at first. The strongest clinical clue for diagnosis is the stereotyped, repetitive, short-duration episodes of unexpected laughter. Diagnosis can also be difficult because EEG tests (electroencephalography) often appear normal or show minor changes or non-specific abnormal findings in children in the early stages, and MRI's require a specific protocol to focus on the area of the brain where HH's are present. Hamartomas are considered benign, which means they do not usually get larger.

How Common is Hypothalamic Hamartoma Syndrome?

While the exact number of people with hypothalamic hamartomas is not known, HH is estimated to occur in 1 out of 200,000 children and teenagers worldwide. This estimate, which may be low since HH is hard to detect, suggests that there are about 30,000 in the world living with HH.

What causes HH syndrome?

We do not yet know the cause in all cases of HH but believe genetic factors contribute to many of them. A small percentage of children with HH inherit the condition from a parent (known as 'Pallister-Hall syndrome'). Genetic testing of these patients reveals abnormalities of the GLI3 gene that provides important signals to cells during development. For the majority of HH cases that are not inherited from a parent, and instead arise randomly in the child (known as 'non-syndromic HH'), about one-third have been shown to also have an abnormality in the GLI3 gene, or a related gene with a similar function during development. Abnormalities in other types of genes may cause HH and there is active research underway to find these. It is suspected that this may include genes important for the function of hair-like structures (known as 'cilia') that project from the surface of cells. Defects in these cilia genes disrupt normal development and have already been associated with more than 30 human diseases (known as 'ciliopathies'), and it is likely that HH is a ciliopathy disease too.

Genetic counselling is recommended for all individuals with Pallister-Hall syndrome where the GLI3 gene abnormality has been transmitted from a parent to their child because the same abnormality can be passed on to other children. It is not currently recommended for non-syndromic cases however that may change depending on further research into the cilia gene abnormalities as at least some of these are known to be transmitted to children. Determining the underlying genetic cause of HH may lead to development of new treatments.

When do symptoms first appear?

Gelastic – or laughing – seizures are usually the first indicator of HH. Gelastic seizures often occur in infancy and may not be recognized as seizures for years because of the way they look. Gelastic seizures are so named because they may look like bouts of uncontrolled, often mirthless laughter or giggling. Often, once parents hear a description of a gelastic seizure, they realize they have been happening for a while. Often the seizures go unrecognized until some other seizure type appears. Individuals can also have learning disabilities, developmental delays, emotional outbursts or rages, or cognitive issues beginning in early childhood.

What are the types of seizures seen in HH syndrome?

Gelastic seizures are almost always the first seizure manifestation of HH. Gelastic seizures start in infancy in more than a third of individuals. They are often forced and the person cannot stop them from happening. Most people do not feel happy and in fact, may feel anxiety and panic when they are forced to laugh at inappropriate times. Other common features of a gelastic seizure are:

- The person may look startled or even have a look of panic or fear.
- There can also be an unpleasant feeling in the stomach (like butterflies), a tickling in the chest or headache. Lip smacking or frequent swallowing may be seen.
- The person may stare. Their eyes may seem vacant and move up and to one side.
- There often is a slight smile that seems a bit forced and laughter or grunting that seems unusual or not appropriate at that time.
- Gelastic seizures may be triggered by loud noises or sudden actions.
- These seizures can occur many times a day; in some cases, hundreds of times daily.

Other types of seizures (see below), triggered by the HH, appear later.

How may the epilepsy change over time?

The progression to uncontrolled epilepsy typically occurs between the ages of 4 to 10 years. Seizures can be of both focal and generalized types. Focal impaired awareness seizures (previously called complex partial seizures) commonly involve staring, loss of awareness and automatic movements of the face and limbs. Generalized seizures include absence, atonic, tonic, and tonic-clonic seizures.

Is HH syndrome linked to any other syndromes or conditions?

- Pallister-Hall syndrome (a genetic condition that may include extra fingers or toes, changes in hormone function, and changes in the way other parts of the body develop).

What other problems apart from epilepsy, affect people with HH syndrome?

- Cognitive problems, such as changes in thinking, memory or attention.
- Sudden episodes of rage (called hypothalamic rages).
- Other types of changes in mood or behaviour.
- Endocrine issues, especially precocious puberty.

What are the treatment options for HH syndrome?

Seizures in people with HH often do not respond well to anti-seizure medications (ASM). Although the prescription of ASM is indispensable, overtreatment should be avoided. Treatment now focuses on either disconnecting the hamartoma, or ablating (destroying) or removing it, controlling or eliminating seizures, and stopping the decline of cognitive function.

What types of surgery are available?

The type of surgery recommended is chosen based on a number of factors, such as the size and location of the hamartoma, seizure frequency, and cognitive function. A large hamartoma typically requires surgeries in different phases or a combined approach. Surgical treatments may include MRI-guided laser therapy, Gamma Knife radiosurgery, stereotactic radiofrequency thermocoagulation, endoscopic resection and transcallosal resection. It is of primary importance that the clinical and the neurosurgical teams should have experience in treating HH patients.

Who should be a part of the medical team?

Managing the challenges often requires a team of knowledgeable medical specialists, including neurologists or epileptologists, neurosurgeons, neuropsychologists, endocrinologists, and pediatricians. These can be found at comprehensive epilepsy centres

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