Hypothalamic Hope Hamartomas
Giving Hope. Getting Answers.

Hypothalamic Hamartoma Syndrome

(Also known as: HH)

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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Patient groups:

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