Hypothalamic hamartoma

Hypothalamic hamartomas (HH; hamartoma: an abnormal conglomeration of cells normally found in the same area) AKA diencephalic hamartomas or hamartoma of the tuber cinereum.

Rare, non-neoplastic congenital malformations arising from inferior hypothalamus or tuber cinereum (floor of the third ventricle between the infundibular stalk and the mammillary body). May occur as part of Pallister-Hall syndrome (genetics: AD inherited defect in GLI3 gene, resulting in abnormally short GL13 protein, which participates in normal shaping of many organs).

Hypothalamic hamartomas are nonneoplastic overgrowths of normal appearing tissue comprised of disorganized neurons and glia that are lacking the enlarged “balloon cells” characteristic of focal cortical dysplasia [1].

They are non-progressive lesions and do not expand, spread or metastasize to other locations.

Classification

Giant Hypothalamic Hamartoma.

Epidemiology

Hypothalamic hamartomas are relatively rare. Population-based research has shown that HH with epilepsy occurs in 1 of 200,000 children and adolescents. The prevalence of HH with only precocious puberty is unknown. At least for HH with epilepsy, males appear to have a slightly higher risk than females (approximately 1.3 to 1 ratio). HH occurs worldwide, without any obvious geographical concentration of cases. It is currently felt that all ethnic groups are at equal risk. There are no identified maternal risk factors or fetal exposures that increase the risk of HH.

Causes

The underlying cause remains unknown. Over 95% of cases are sporadic (that is, there is no prior family history and the identified patient remains the only affected individual in the family). A defect in factors that regulate fetal development of the hypothalamus is most likely.

However, HH can also occur in patients with identified genetic disorders. Of these, Pallister Hall syndrome accounts for the vast majority.

Pathology

Histologically, hypothalamic hamartomas resemble normal hypothalamic neurons, although some dysplastic neurons and glial cells have also been described

They are thought to arise from anomalous neural migration between 35 and 40 days in utero (time of hypothalamic formation).

Clinical features

There is tremendous diversity in the type and severity of symptoms from patient to patient. However, symptoms are apparent during childhood in the overwhelming majority of patients. Although significant overlap exists, two clinical phenotypes of HH are recognized:

Central precocious puberty

Epilepsy and related neurobehavioral symptoms

Hypothalamic hamartomas may be associated with gelastic seizures, focal seizures, and a generalized epileptic encephalopathy, with severe seizures and cognitive and behavior decline. Despite earlier views to the contrary, good evidence now exists that all these clinical features are caused, directly or indirectly, by the hamartoma.

Diagnosis

MRI

MR imaging is sufficient to establish (or rule out) the diagnosis of HH. However, there are important considerations to imaging for HH. Imaging must be technically adequate to permit detailed visualization of the hypothalamus. Movement artifact resulting from restlessness of the patient within the scanner can obscure small HH lesions. Accordingly for children or other patients with limited cooperation, a sedated study is recommended. Additionally, the choice of specific imaging sequences is also important.

The study include a coronal T2 fast spin echo (FSE) sequence, with thin slices and no gap or space between slices. Lastly, the radiologist should be informed that HH is one of the clinical conditions under consideration, so as to include careful inspection of that region of the brain. Most patients (over 90%) have normal brain findings on MR imaging aside from the HH. A small number of patients may have additional abnormalities, such as malformations of cortical development.

T1: isointense to cerebral cortex

T1 C+ (Gd): no contrast enhancement

T2 iso- to hyperintense to cerebral cortex the higher the proportion of glial cells, the higher the T2 signal

MR spectroscopy

reduced NAA/Cr increased myoinositol increased Cho/Cr compared to the amygdala has also been reported [2].

CT

Computed tomography (CT) imaging is not adequate for detecting small HH lesions, and has the added disadvantage of radiation exposure.

Physical signs of precocious puberty require evaluation by an endocrinologist. The hypothalamus and pituitary together produce a number of different hormones, including the reproductive hormones responsible for puberty. Consequently, evaluation of patients with HH should include testing for other factors such as thyroid, adrenal, and growth-related hormones.

Electroencephalography (EEG) testing is routinely performed in patients with epileptic seizures or suspected epileptic seizures, and can be useful in evaluating patients with HH and epilepsy. However, it must be recognized that EEG results may be normal, particularly at younger ages when gelastic seizures are the only seizure type. This includes video-EEG monitoring that captures gelastic seizures. That is, the EEG may show no change even during the actual gelastic seizure event. This is due to the fact that gelastic seizures arise in the HH, and as a structure located deep at the base of the brain, it is distant from EEG electrodes on the scalp. This can lead to incorrect diagnoses.

EEG studies can show abnormal results, particularly in older patients who have developed other types of seizures. A wide variety of findings is possible, and can suggest either focal or generalized disturbances. Consultation with a neurologist experienced with evaluating patients with HH and epilepsy is recommended whenever possible. This expertise is usually available at regional epilepsy referral centers.

Neuropsychological testing can be an important tool for patient management, particularly those with HH and epilepsy. These patients are “at-risk” for developmental and cognitive deficits. For some patients, these difficulties may be progressive, with deterioration or worsening in their level of function. Neuropsychological testing can help define the pattern of functioning (i.e., strengths and weaknesses) in the various skills of higher brain functioning (such as memory, language, problem-solving, etc). This can help with adaptive therapies and provides a baseline for those patients who may be declining. Additionally, neuropsychological testing is very important for those undergoing surgical intervention in order to clarify changes (for either the better or worse) that may accompany surgical treatment.

The basic cellular mechanisms responsible for seizure onset within HH are unknown.

With intra-operative microwire recordings of single neuron activity to measure the spontaneous firing rate of neurons and the degree of functional connection between neurons within the tumor.

Treatment

Hypothalamic hamartoma treatment

Outcome

They grow in proportion to normal brain growth, and consequently their relative size to the rest of the

brain is the same for the lifetime of the patient when viewed with serial imaging.

Case series

Hypothalamic hamartoma case series.

Case reports

Hypothalamic hamartoma case reports.

1)
Coons SW, Duane DC, Johnson EW, Lukas RJ, Wu J, Kerrigan JF. Etiology and epileptogenesis of hypothalamic hamartomas: opening the door. Barrow Q. 2004;20:34–41.
2)
Amstutz DR, Coons SW, Kerrigan JF et-al. Hypothalamic hamartomas: Correlation of MR imaging and spectroscopic findings with tumor glial content. AJNR Am J Neuroradiol. 2006;27 (4): 794-8. AJNR Am J Neuroradiol